COLUMBIA LIBRARIES OFFSITE
HEALTH SCIENCES STANDARD
HX64166708
RC201 .M912 The therapy of syphi
RECAP

THE THERAPY OF SYPHILIS

MULZER

RC 201 M912

Columbia University
in the City of New York

COLLEGE OF PHYSICIANS
AND SURGEONS

Reference Library
Given by
Dr. William S. Gottheil.

Digitized by the Internet Archive
in 2010 with funding from
Open Knowledge Commons

http://www.archive.org/details/therapyofsyphili00mulz

THE THERAPY OF SYPHILIS

ITS DEVELOPMENT AND PRESENT POSITION

BY

DR. PAUL MULZER

OF BERLIN

WITH A PREFACE BY

PROF. P. UHLENHUTH, M.D.

PRIVY COUNCILLOR

TRANSLATED BY

A. NEWBOLD

NEW YORK

REBMAN COMPANY

1123 BROADWAY

Entered at Stationers' Hall

All rights reserved

DEDICATED

WITH THE GREATEST RESPECT

TO

HIS ROYAL HIGHNESS

LOUIS FERDINAND, M.D.

PRINCE OF BAVARIA

PREFACE

It is not to exact scientific research that we owe a number of the best and most effectual of our drugs used in combating infectious diseases, but instead to rough empiricism. I may mention here quinine, iodine, salicylic acid, mercury, and arsenic.

The phrase " practice surpasses theory " has even now a certain justification; and, indeed, in the present era of exact experimental therapy, we cannot quite dispense with these unscientific-sounding words. The difference between now and formerly only consists in the fact that, in many infectious diseases against which we wage war, armed with these drugs, we have become acquainted with the instigators of the disease; further, we can to a certain extent transfer these to animals, and conse-

quently carry out our experiments upon them. These latter, however, are now performed quite differently to what they were formerly, for, as the result of our exact knowledge, we can ocularly observe and follow under the microscope the destructive action of many drugs upon the microparasites in question. This is an enormous advance, and is highly gratifying to both physician and researcher, who are thus able to realise the attractive and fertile stage the study of chemotherapy has attained.

From the empirical a causal therapy has been evolved. It is also conceivable that the knowledge of the expert and purposeful application of this expedient is due first of all to bacteriological science, the duty of which consists, not only in searching for the causes of infectious diseases, but also in destroying the exciters both inside and outside the human and animal body.

This applies to-day especially to aromatic

arsenic preparations, which are of paramount medical interest; their efficacy has been tested in bacteriological laboratories, and they have been proved to be powerful weapons in the struggle against diseases due to trypanosomes and spirochætes.

In relapsing fever and syphilis—the most dreaded human spirochæte diseases—these arsenic preparations have already yielded many gratifying results. Nevertheless, we must acknowledge that even now we are far from possessing an ideal specific drug, as, apparently, with nearly all the arsenic preparations which have been employed so far, there is a certain neurotropic action. At the same time, we must not abandon aromatic arsenic preparations in the treatment of syphilis, especially as they are effective in those cases in which iodine and mercury fail.

In the book before us, by Dr. Mulzer, my esteemed colleague in the domain of experimental syphilis, the general practitioner will be enlightened as to the present

position of modern specific therapy; he will be shown what was formerly accomplished, and at the same time its development up to the present day will be demonstrated to him.

As the work of the Imperial Health Bureau paved the way for this improvement and practically promoted it by the discovery of the *Spirochæta pallida*, by researches in experimental syphilis of rabbits, and, above all, by the construction and development of the experimental basis of the organic arseno-therapy of spirilloses, and especially of syphilis, it is a particular pleasure to send this book on its way with a foreword and to associate this with the wish that arseno-therapy in its present form and future evolution may bring a blessing to suffering humanity.

PAUL UHLENHUTH
(*Imperial Health Bureau*).

BERLIN,
GROSS LICHTERFELDE,
December 16, 1910.

INTRODUCTION

After F. Schaudinn discovered the *Spirochæta pallida* at the Imperial Health Bureau, in 1905, and, in common with E. Hoffmann, reported on the constant appearance of this peculiar micro-organism in the most varied infectious products of specific disease, the pendulum of syphilitic research swung forward unexpectedly and vigorously. The epoch-making communications of Schaudinn and Hoffmann were further tested by many researchers. Within a short time numerous works appeared which confirmed and extended these results, so that the probability of the *S. pallida* being the exciter of syphilis became greater and greater. It was soon proved that specific disease must exist in the organism if one could testify to the certain presence of the

S. pallida. If found in an ulcer or erosion, which could not be positively diagnosed clinically, this might be pronounced to be a primary syphilitic affection. Later, the appearance of secondary phenomena always confirmed the accuracy of this diagnosis. Subsequently, when syphilis was experimentally produced in animals, it was regularly possible to prove the presence of the *S. pallida,* and to therapeutically influence this form of disease by means of specific remedies. All these facts have taught us that the *S. pallida* is really the exciter of syphilis.

These results were first practically applied in confirming the diagnosis of syphilis. To Erich Hoffmann is due the service of having again and again referred to the extraordinary diagnostic importance of the presence of *S. pallida* in doubtful cases of disease.

A further advance in modern syphilitic research is indicated by the introduction of serum diagnosis by A. Wassermann,

A. Neisser, and C. Bruck. Supported by the experience and observations of numerous teachers, there is no longer any doubt that the positive result of the Wassermann test in all probability indicates that the individual, whose blood-serum gives this reaction, must at some time have suffered from specific infection. A preliminary condition for such a conclusion is naturally skill in carrying out the reaction and an irreproachable technique.

Some time before the discovery of the *S. pallida* Metschnikoff and Roux had succeeded in transmitting syphilis to apes. Acting on this discovery, it was possible for A. Neisser and his collaborators, after working for years in Batavia, to experimentally solve upon apes many highly valuable problems of the pathology and therapy of syphilis. Bertarelli, Levaditi, Parodi, Hoffmann, Löhe and the author, Uhlenhuth, and Weidanz, Grouven, Truffi, and other researchers also succeeded later in experimentally infecting rabbits with

syphilis ; these results, however, were regarded more or less as accidental and exceptional. Uhlenhuth and I, after systematically arranged experimental studies on syphilis of the scrotum in rabbits were the first to demonstrate that these animals, more than all others, including the lower apes, are specially adapted for this kind of experimental research. It is on this fact, which was later also confirmed by other authors — such as Truffi, Menzincesku, Tomasczewski, and M. Koch—that the results which indicated the modern chemotherapy of syphilis were finally based.

CONTENTS

	PAGE
PREFACE BY PRIVY COUNCILLOR UHLENHUTH	v
INTRODUCTION (DISCOVERY OF THE *Spirochæta pallida*, WASSERMANN REACTION, EXPERIMENTAL SYPHILIS) - - - -	ix
INFLUENCE OF THE RESULTS OF SYPHILITIC RESEARCH UPON THE FORMER MERCURIAL THERAPY OF SYPHILIS - - -	1
CHEMOTHERAPY OF SYPHILIS:	
I. ATOXYL - - - - -	12
II. ARSACETIN (EHRLICH) - - -	27
III. ATOXYLATE OF MERCURY (UHLENHUTH)	29
IV. HECTINE - - - - -	37
V. SOAMIN - - - - -	38
VI. ARSENOPHENYLGLYCIN - - -	40
VII. DIOXYDIAMIDOARSENOBENZOL (EHRLICH-HATA "606") - - -	44
1. CHEMICAL CONSTITUTION, EXPERIMENTS ON ANIMALS - - -	45

CONTENTS

PAGE

VII. DIOXYDIAMIDOARSENOBENZOL—*continued:*

2. SUSPENSION OF SOLUTIONS WHICH ARE READY FOR USE - - - 50

(*a*) ALKALINE SOLUTIONS - - 51

(*b*) NEUTRAL EMULSIONS - - 58

(*c*) KROMAYER'S PARAFFIN EMULSION 65

3. TECHNIQUE OF INJECTION - - 71

(*a*) INTRAMUSCULAR INJECTION - 71

(*b*) SUBCUTANEOUS INJECTION - 73

(*c*) INTRAVENOUS INJECTION - - 75

4. DIRECT LOCAL SECONDARY EFFECTS OF THE INJECTION - - 81

5. EFFECT OF ARSENOBENZOL UPON THE ORGANISM IN GENERAL - - 86

6. EFFECT OF ARSENOBENZOL ON SYPHILITIC DISEASES OF THE PRIMARY, SECONDARY, AND TERTIARY PERIODS - - - - 89

(*a*) PRIMARY AFFECTIONS - - 92

(*b*) EARLY STAGE OF SECONDARY SYPHILIS - - - - 98

(*c*) THE LATE STAGE OF SECONDARY SYPHILIS AND TERTIARY SYPHILIS 110

(*d*) MALIGNANT SYPHILIS AND ULCEROUS TERTIARY FORMS RESPECTIVELY - - - - 119

CONTENTS

PAGE

VII. Dioxydiamidoarsenobenzol—*continued*:

(*e*) Treatment of Syphilitic Diseases of the Eyes with Arsenobenzol - - - - 122

(*f*) Syphilis of the Internal Organs - - - - 126

(*g*) Meta- and Para-Syphilitic Diseases, including Tabes and Paralysis - - - 128

(*h*) Hereditary Syphilis - - 133

7. Dosage - - - - 139

8. Influencing the Result of the Wassermann Reaction by Means of Treatment with Arsenobenzol - - - - 141

9. Relapses - - - - 149

10. Secondary Effects - - - 172

11. Epicrisis - - - - 196

Literature - - - - - 205

Index - - - - - - 225

Authorities referred to - - - 245

THE THERAPY OF SYPHILIS

INFLUENCE OF THE RESULTS OF SYPHILITIC RESEARCH UPON THE FORMER MERCURIAL THERAPY

The experience of a century has taught us that, of all the drugs used in the treatment of syphilis, without doubt mercury is the most powerful and effective. In earlier times many errors in its therapeutic application, from ignorance of cause and effect, often resulted in the serious injury of the individual, who had been treated too drastically. If, in consequence, this drug is to-day still discredited in many lay circles, we know that, with expert medical application and control, mercury is at the present time the sole drug capable of effecting

the definite cure of syphilis, even if this is not so in all cases. The accuracy of this statement is testified to by the fact "that severe tertiary symptoms appear most frequently in untreated or inadequately treated cases, whereas, on the other hand, the best protection against this is early, energetic mercurial treatment" (E. Lesser).

I will not go into further details here, as to the special indications for this therapy, and respectively as to the different mercurial preparations and their application in the individual stages of syphilis. I will merely briefly recapitulate when we began the general treatment—*i.e.*, until the discovery of the exciter of syphilis. There were two opinions with regard to this. In the one, the specific treatment was begun as soon as possible—*i.e.*, immediately after the recognition of the primary affection; in the other, it was believed that it was necessary to wait until the appearance of the first secondary symptoms indicated a generalisa-

tion of the syphilitic virus ; the adherents to this view included some of our most celebrated syphilidologists. In this therapeutic procedure, they relied upon their experience and that of other teachers, who considered the action of mercury was most lasting in the general syphilitic stage, and that it had never been possible to succeed in arresting the disease by early treatment, and thus prevent an outbreak of general infection. Above all, however, it was believed that one must wait until the eruption of roseola appeared, because it was only then that one could diagnose syphilis with absolute certainty, as even the most experienced teacher might be deceived by the manifold and frequently uncharacteristic forms of the phenomena of the primary affection.

This hesitation disappears now that we are capable of obtaining the proof of the presence of the *Spirochæta pallida* in doubtful cases of diseased tissue, occasionally after repeated careful examinations,

and of recognising these absolutely as primary syphilitic lesions.

Further, animal experiment has also removed the objection that it is only with the outbreak of the secondary symptoms that the virus is spread over the organism, and is then more accessible to general specific treatment. Hoffmann was able to prove experimentally that the blood of syphilitics induced syphilis in apes, which had been inoculated with it, about the sixth week after the infection, therefore several weeks before the outbreak of the secondary symptoms. Neisser was able to demonstrate that the internal organs of apes already contained syphilitic virus at the time of the appearance of the primary affection, and, indeed, mostly much earlier, from the fact that, by inoculating the spleen-liver-bone-marrow pulp of an animal diseased in this way on to other healthy animals, typical forms of syphilitic disease could be induced. In the same way, Uhlenhuth and I were able to confirm this fact

by the primary inoculation syphilis of rabbits. Another circumstance which must be taken into consideration as testifying to this is the fact that, according to the statement of most authors, the Wassermann reaction shows a positive result in nearly half the cases in the primary stage.

From the clinical observations of Holländer, Hoffmann, Thalmann, and others, we know, however, that in the so-called "early treatment" of syphilis by excision of the primary affection, with subsequent drastic doses of mercury, even if perfect cure is extremely rare, it is possible to diminish the intensity of the further course of the disease to some extent.

It is, therefore, necessary for the practitioner to begin general treatment as soon as ever syphilis has been diagnosed—*i.e.*, directly it has been possible to prove the presence of the *S. pallidæ* in the suspected diseased material. By extending the excision into the healthy part as far as possible, one must endeavour to remove the primary

affection, so as not to renounce the possibility of arresting the syphilis, or at least of preventing a further immigration of the spirochætes into the organism from here. Where this is not possible, in consequence of the anatomical position, we must try to destroy them by cauterisation, hot air treatment, or by covering with mercurial plaster, and finally annihilate the spirochætes everywhere, by injections of soluble mercurial or arsenical preparations (for example, hydrargyrum oxycyanatum, atoxyl, Ehrlich-Hata). "From the point of view of prophylaxis also, it is very desirable to reduce the chancre as soon as possible, and so avoid its being the source of fresh infections" (Hoffmann).

From my experience, I find we do not select our strongest mercurial preparations at the beginning of general treatment, so that there is a possibility of increasing the dose in individual cases. But instead, we try to augment the intensity of the preliminary treatment by its longer duration.

The animal experiments of Neisser and his collaborators have demonstrated that mercury is a direct remedy for specific disease, and, indeed, not only of manifest syphilis, but also in the latent stages. From this Neisser infers the justice of our former therapy—namely, that in human syphilis mercury is not to be administered solely as a systematic remedy, but also in those cases where clinically we can determine no symptoms, but, nevertheless, know, partly from general experience and partly from the serum diagnosis, that there is still specific poison in the body. Further, if we reflect that in most of the forms of disease spirochætes are present during the second period, and are therefore capable of remaining for a very long time in the body, all these facts testify fully to the justice —indeed, the necessity—of chronic intermittent treatment of syphilis.

With regard to the question as to how far the result of the Wassermann reaction should influence our therapeutic treatment,

this has not been explained at the present time. As long as we do not definitely know the genuine nature of this reaction, a complete solution of the problem cannot be anticipated. The majority of authors agree that the positive result of the Wassermann reaction indicates with absolute certainty that active syphilitic virus is still present in the organism. It naturally follows that, in every case in which the serum reaction gives a positive result, anti-syphilitic treatment should be introduced, quite immaterially whether manifest symptoms are present or not. Other teachers, amongst whom I include myself, acknowledge, it is true, that the specific therapy exercises a certain influence upon the result of the reaction, but they believe that this has too little constancy and proportion to require a special therapy to which the organism is not quite indifferent, especially in the more advanced cases of syphilis. In my opinion, the practical value of the Wassermann reaction lies principally in the

diagnostic domain, and respectively of differential diagnosis. Therapeutically this reaction can be taken advantage of, in that a positive result of the same proves, with a probability bordering on certainty, that specific infection has occurred in the individual whose blood gives this reaction. We must then make an exact anamnesis of the course of the disease and of former treatment, our further therapeutic measures being first of all dependent on this result. The same thing applies, certainly in a far less degree, to an occasional negative result of the Wassermann reaction. In itself this naturally proves nothing. It is only when the examination of the blood, repeated at varying periods, has always given an irreproachable negative result, and there are no certain indications of syphilis present, either anamnesically or clinically, that the negative result of the reaction may be considered diagnostically. Otherwise it cannot in any way influence the treatment of the practitioner, either

with regard to prognosis or therapy, as we know that, even when syphilitic symptoms are manifest, a negative result of the Wassermann reaction is not always excluded. In my opinion, it is incorrect that specific treatment, and respectively its duration and intensity, should be undertaken under the constant control of the Wassermann reaction, its effect and duration being made dependent upon the occasional result of the Wassermann test, as is done by some authors. For, according to my researches, the result of the Wassermann reaction may often fluctuate backwards and forwards during a mercurial cure.

Besides these results, which are valuable for modern mercurial specific therapy, a whole series of other important questions have been explained by syphilitic research, or their solution has been approached very closely, and of these I will briefly mention a few. Finger and Landsteiner, Neisser and Hoffmann succeeded in proving the infectiousness of gummata from observa-

tions on animals. Finger and Landsteiner, Neisser, Tomasczewski, Uhlenhuth, and I were able, by animal experiment, to contradict the dogma of absolute and permanent immunity set up by Ricord, which a single attack of specific infection is supposed to bestow, but which, on the ground of clinical observations, had appeared doubtful to some of his contemporaries and also to many later teachers. Questions of individual prophylaxis were also touched upon, and enabled us to recognise a good, but not absolutely certain, protection against specific infection in the administration of the 30 per cent. calomel salve (Metschnikoff and Roux). By means of comprehensive serological examinations, the accuracy of the law of Colle and Profata was determined by Bruck, Boas, Blumenthal, Michaelis, the author, and others.

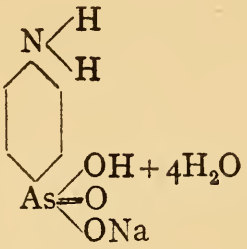
The triumph of syphilitic research, however, consisted in its being the basis of the modern chemotherapy of syphilis.

THE CHEMOTHERAPY OF SYPHILIS

I. ATOXYL.

THE constitution of this preparation, which was originally described as meta-arsenic acid anilide, was first explained by P.Ehrlich and Bertheim. They proved that by heating the arsenic acid anilin, under a base corresponding to the sulphanilic acid presentation, para - amino - phenyl - arsenic acid is formed. This acid is very difficult to dissolve in water (1 : 255) and by other usual methods of solution, but will dissolve without decomposing in caustic and carbonic acid alkalies. By dissolving in the estimated quantity of alcohol, the monosodium salt, *p*-aminophenylarsenic acid, atoxyl is formed, the constitution formula

of which is given as follows by Ehrlich and Bertheim :



The crystalline watery content is not constant, but instead varies with the manner of preparation, and the condition of crystallisation thus caused.

Atoxyl is a crystalline powder without either colour or smell, with a cool, weakly saline taste. On heating it decomposes slowly, gradually assuming a brown colour without melting. It is soluble in 4·3 parts water at 20° C. The aqueous solution saturated at this temperature contains 18·8 per cent. of atoxyl. The solubility in water is greatly increased by a heightened temperature. It is very difficult to dissolve atoxyl in alcohol. The solutions assume a brownish-yellow colour if they stand in

the air and light, and similarly if they are boiled for long, when they lose their curative power, and become toxic instead. If the solution is to be sterilised, it should be heated in sterile vessels for two minutes at 70° to 80° C., or it should be filtered after Uhlenhuth's method, by means of Berkefeld's bougies. In this way, a sterile preparation which is perfectly irreproachable is obtained.

The aqueous solution has a weakly acid reaction. If it is transposed with diluted acids, then the atoxylic acids will be precipitated in thick white flakes, which dissolve very easily in the overflow, but not in that of acetic acid.

F. Blumenthal was the first to employ the new drug in medical practice, in 1902. By means of valuable pharmacological researches, he proved the relative non-toxicity of the preparation, and drew attention to its favourable qualities. According to the reports of F. Blumenthal, atoxyl is forty times less toxic than Fowler's

solution. Further, he considers this preparation has the advantage over Fowler's solution and other arsenic preparations, in that the arsenic from this atoxyl, although bound fast to the benzol nucleus, is split up in the organism, and so acts *in statu nascendi.* The researches of Blumenthal and Jakoby place the principal action of atoxyl in the blood, where it either acts directly by splitting up the arsenic acids, or may appear catalytically in function, while acting upon such in the cure of important processes.

It was through the English physician W. Thomas that atoxyl, which had already been found to be tolerated in the treatment of diseases of the blood and of the nervous system, as well as in various cutaneous affections, was introduced into the therapy of trypanosome diseases (1905). Thomas and Breinl obtained excellent results in the experimental infection of rats, mice, rabbits, etc., with the trypanosomes of surra, nagana, sleeping sickness, etc.

The results of the experiments of Mesnil, Nicolle, and Ehrlich were less favourable; independently of Thomas, they administered atoxyl to animals infected by the tsetse fly, *surra* and *mal de caderas*. Atoxyl, recommended by Thomas, was further tried with advantage by Kopke, Broden, Rodhain, and others in the treatment of sleeping sickness; but it was Robert Koch who first carried out a systematic and purposeful atoxylic cure, when the material at hand was on a large scale. Amongst other things, R. Koch was able to prove that, eight hours after the injection of atoxyl, the trypanosomes had already disappeared from the lymphatic glands and from the blood. Moreover, with the disappearance of the trypanosomes from the lymphatic glands, a distinct improvement took place in the patient's condition.

Instigated by the reports which had been published, and particularly by Koch's favourable results, Uhlenhuth commenced some experiments at the Imperial Health

Bureau, Berlin, in 1906, which consisted first in treating dourine disease with atoxyl.

As has been reported by Uhlenhuth and his collaborators Hübener, Woithe, and Bickel, the results of the protective and curative experiments undertaken in this direction were favourable.

Further, the authors recorded that certain considerations had led them to try atoxylic treatment in other protozoal diseases also. The opinion laid down by Schaudinn, that many spirochætes represent special stages of development of trypanosomes, caused them first of all to try atoxyl in spirillosis of fowls.

The exciter of this disease is the *S. gallinarum*, which was discovered by Marchoux and Salimpeni at Rio de Janeiro, in 1903. The disease, which frequently sets in as septicæmia with a fatal result, begins with high fever and diarrhœa. The animals soon become somnolent, and sometimes succumb from paralysis and also from spasms. If fowls are infected with blood

containing spirochætes, the parasites can generally be detected in the circulation on the second day after infection; they increase rapidly up to the fourth to sixth day, when they can be found in the blood in great convoluted colonies. The crisis sets in on the seventh to ninth day; the spirochætes disappear spontaneously from the circulation, and the animals are then immune, if they do not succumb to the disease. A natural immunity is obviously rare.

Here, also, the authors succeeded in proving in an absolutely trustworthy manner that atoxyl exercises a protective and curative action in spirillosis of fowls; that it is capable of destroying the spirochætes in the blood of the diseased fowls and of causing their disappearance.

Uhlenhuth, Gross, and Bickel conclude their communications, which appeared in No. 4 of the *Deutschen Medizinischen Wochenschrift*, January 24, 1907, with the following words: "As atoxyl has a destructive

action on the most varied trypanosomes, it is easy to reflect that it may develop a similar action to that of the *S. gallinarum* on various other spirochætes. Appropriate experiments with the spirochætes of relapsing fever and of syphilis are in progress, the positive result of which would be of practical importance in combating these diseases."

It was soon possible to report on the results of researches of this description. The experimental work of Uhlenhuth and his collaborators in relapsing fever of mice and rats did not, it is true, enable one to come to a definite conclusion as to the efficacy of these preparations in this disease, on account of their toxicity for these animals; but, on the other hand, the experiments undertaken by Glaubermann at Moscow, at the instigation of Uhlenhuth, in Russian relapsing fever, were on the whole favourable. It seemed most important to Uhlenhuth, however, that atoxyl should be tried in the spirochæte disease

of most frequent occurrence — namely, syphilis.

As long ago as December, 1906, Uhlenhuth, with Hoffmann, Roscher, and Weidanz, had endeavoured to obtain a definite answer to the question whether atoxyl exercised a direct influence on the process of specific disease. In syphilis of apes, as well as of rabbits (disease of the cornea) the authors actually observed a noticeable prophylactic and curative effect of atoxyl. Equally good results were obtained soon after by A. Neisser, who also proved, by means of experiments on apes, that energetic treatment with atoxyl, which is best when administered in large single doses, has a very marked influence on syphilis. Therapeutic experiments on human subjects at the Lesser Clinique, at Uhlenhuth's suggestion, were extraordinarily successful with the correct dosage, after having failed at first when the dose administered was too small. The results of this treatment are reported in detail

in a work by Uhlenhuth, Hoffmann, Roscher, and Weidanz. Further, Salmon, Lassar, Hallopeau and others shortly afterwards recorded very successful curative results obtained in human syphilis with atoxyl. E. Lesser spoke very favourably of atoxylic treatment of specific disease, which he regarded as equal to the customary doses of calomel in rapidity of result. Of further authors who tested the therapeutic effect of atoxyl on syphilis, and generally obtained good results with it, I should like to mention Hoffmann, von Zeissl, Lesser, Nagelschmidt, Finger, Moses, Darier, Heuck, Balzer, Rouvière, Kreibich and Kraus, Scherber, Rapiport, and others.

If we compile a résumé from these communications, references, and clinical observations in specialist literature, then, according to Salmon, the favourable effect of atoxyl in syphilis is shown :—

1. *As regards the Constancy of the Results.* —The favourable curative effect appeared in all stages of syphilis—viz., primary,

secondary, and tertiary — and was most brilliant in malignant forms.

2. *As regards the Rapidity of the Action of the Drug.*—After a few injections, chancres diminish and are absorbed, the hardness often disappears remarkably quickly. Fresh roseola, maculo-papulous exanthema, impetigo capitis disappear after ten to fourteen days, psoriasis palmarum after twelve days. The exanthema becomes paler until it is invisible. Papules lose their redness, and, with the absorption of the plastic exudation, flattening, and typical browning (regressive metamorphosis) is evident. Ulcerations close and skin over, annular syphilides dry up, and gummatous infiltrations yield to the treatment in a similar way. Papules, plaques, tuberculous syphilides, tertiary ulcers, diminish rapidly and generally heal over. The headache, which is characteristic of syphilis, often ceases surprisingly rapidly (eighteen hours) after the first injection, the dysphasia and dysphagia of angina syphilitica decrease

after two to three days. According to Darier and others, iritis syphilitica can also be very favourably influenced by treatment with atoxyl.

Cases which are refractory to mercurial treatment, or are only slightly influenced by it, such, especially, as cases of syphilis ulcerosa præcox (malignant syphilis), generally react rapidly and promptly to atoxyl.

3. *As regards the Favourable Effect on the General Condition.*—The patients feel well, and nearly all of them increase considerably in weight.

Unfortunately atoxyl did not subsequently fulfil the hopes which had been centred on it for the therapy of syphilis. The observations on atoxylic resistance, to which Ehrlich first referred, and the practical experience gained in combating syphilis, showed that favourable results could only be obtained with large doses of atoxyl. These doses, however, approached pretty closely to toxic ones, and undoubtedly there was danger that with them the limit of

isotonicity of the preparation, which varies in individual cases, might be exceeded. That this was actually done in the therapeutic administration of atoxyl was proved by observations of injury to the central nervous organs (transitory visual disturbances extending to blindness, and respectively total atrophy of the visual nerves).[1]

In order to prevent relapses, it was necessary to repeat the application at short intervals, and thus the danger of overdosage was still further increased. After the cases of blindness which were first observed in the treatment of sleeping sickness had been reported, naturally the general administration of atoxyl in syphilis had to cease. Uhlenhuth himself was the first to demand this, and wished to reserve the employment of atoxyl for those cases which had proved refractory to mer-

[1] Schanz assumes that this process in the visual nerves must have its origin far from the bulbus, as for a long time the ophthalmoscope gave a negative result, even if the visual disturbances were already extensive.

cury, or had been only slightly influenced by it.

In all the cases of visual disturbance observed, it was possible to regularly build up the distinct progress of this disease, and give sharply-defined pictures of the disease and development of atoxylic blindness respectively. According to Sowade, its individual phases were presented as follows :—

1. Beginning with "cloudiness" or "a veil before the eyes."

2. Intense diminution of the visual power within a few days and weeks.

3. At first there were no changes in the fundus oculi, and often it was only after months that there was perceptible atrophy of the papilla of the optic nerve, without previous neuritic phenomena. Contraction of the vessels of the retina.

4. Frequent maintenance of the normal papillary reaction.

5. As a rule, impossibility of arresting the advance of the affection.

By means of experimental researches on rabbits and dogs, Birch-Hirschfeld and Köster proved that if atoxyl was administered for a long time until the death of the animal, the optic nerve microscopically showed disintegration of the medullary sheath over the entire transverse section.

It was thought at first that these toxic secondary effects of atoxyl were due to chemical impurities, and attributable to the German preparation. A change in the production of the preparation, however, did not result in any noticeable diminution of its toxicity.

In order that the undoubtedly favourable specific action of atoxyl in the treatment of trypanosome diseases and syphilis need not have to be abandoned altogether, especially in cases in which Hg and other drugs fail, various combinations were tried of atoxyl with other preparations or alterations of the chemical structure of atoxyl, which were supposed to be less toxic in their effects. Thus we have:—

II. ARSACETIN (EHRLICH),

which was obtained from atoxyl by chemical changes. It is the salts of sodium of the acetyl combination of *p*-aminophenylarsanilic acid of sodium.

Arsacetin is represented by a white powder; the crystalline water contains three to four molecules, and dissolves easily in cold water at 10 per cent., in hot at 30 per cent. It does not decompose on boiling, and has been proved to be constant throughout (according to Sowade), even when heated in an autoclave for an hour and at 130° C.

It has been pharmacologically determined by Ehrlich, Browning, Uhlenhuth, and Salmon that healthy, as well as diseased, animals can tolerate much higher doses of arsacetin than they can of atoxyl.

Neisser states that it has been proved experimentally that, in the trypanosome and spirilla diseases of various animals, arsacetin is at any rate found to be quite as good as atoxyl.

Neisser and the few teachers who have tested this preparation therapeutically, have obtained a good effect on the diseased syphilitic tissue with it, similar to that of atoxyl. Here, again, the tertiary forms of the disease, as well as malignant syphilis, appeared to be specially favourably influenced by the drug. The experience of Heymann and Sowade, however, showed that, in the majority of cases, the effect of mercury was undoubtedly more certain and durable. Soon after the employment of arsacetin, reports came to hand from different sources of "considerable phenomena of intoxication," such as headache, nausea, vomiting, giddiness, abdominal pain, shooting pains in the extremities, nephritis, and finally visual disturbances (Heymann, Klemperer, Sowade, etc.), from which it appeared that arsacetin, especially with regard to a toxic action on the optic nerve (in Africa, 5 to 10 per cent. atrophy of the optic nerve), was more poisonous than atoxyl (Jenssen, Oppenheim, Paderstein,

Ruele, Hammer, Pflughöft, Borcher). Further, it seemed, as Uhlenhuth reported at the Colonial Congress, 1910, according to the records of Feldmann, that arsacetin exercised a toxic action on the auditory nerves. In Africa, out of fifty-one patients treated with arsacetin, nine became blind and two simultaneously deaf.

As Heinrich has cited, Ehrlich himself is of opinion that arsacetin possesses no advantages over atoxyl in a number of diseases, especially those of syphilis and sleeping sickness, which "to a certain extent are difficult to sterilise." On account of the threatened danger to the eyes, Ehrlich no longer recommended it.

III. ATOXYLATE OF MERCURY (UHLENHUTH) (*P*-AMINOPHENYLARSONATE Hg).

At the Imperial Health Bureau, Berlin, Uhlenhuth, Hübener and Woithe obtained good results in dourine, in experiments carried out by the combined application of atoxyl and sublimate. Further, the

therapeutic experiments in relapsing fever, reported by Manteufel, showed that mercury had a certain therapeutic effect on this spirochæte disease in colloid form. On the basis of these results, and in consideration of the fact that mercury is known empirically to act organically on syphilis and respectively on the spirochætes, the exciters of this disease (Uhlenhuth and Manteufel), Uhlenhuth, at a meeting of the Association of Internal Medicine, Berlin, June 24, 1907, proposed that a combination of atoxyl and mercury should be used for the treatment of syphilis. In trypanosome diseases, treatment with these two drugs had already been recommended by Moore, Nierenstein, and Todd.

Soon, as the results of experiments on animals made with a new atoxylic preparation brought out by the United Chemical Works, Charlottenberg, from Uhlenhuth's formula, Uhlenhuth and Manteufel were able to record good results obtained with this new drug, atoxylate of mercury, which

promised to be of practical importance in the treatment of syphilis.

Both authors first made researches with atoxylate of mercury by experimentally infecting rats with relapsing fever. Although in themselves apparently very unsuitable for such treatment, as they tolerate atoxyl, and mercury especially, very badly, nevertheless, it was distinctly possible to recognise the antiparasitic qualities of the preparation from the experiments.

Further experiments made on spirochætic septicæmia of fowls proved that atoxylate of mercury actually exercised a very energetic action on the spirochætes.

After these preliminary exploratory observations, the authors proceeded to influence experimental syphilis with atoxylate of mercury therapeutically. The effects observed in corneal syphilis of rabbits entirely confirmed the results obtained in the study of spirochætosis of fowls. Uhlenhuth and I succeeded in completely curing three large typical syphilitic ulcers in ten and

eighteen days respectively, two being scrotal ones in rabbits. Later, we were able to confirm these results on a large quantity of rabbits. We simultaneously made the observation that even as soon as twenty-four hours after the first adequate dose no spirochætes at all, or only very few, could be found in the diseased material, and that, after a further twenty-four to twenty-six hours, they had entirely disappeared.

It is evident from the above, that in these healing processes we have to do with a specific action of this preparation on the spirochætes themselves, as was already shown by Uhlenhuth and others in their experiments on fowls suffering from spirochætes; for that tissue was first influenced therapeutically which contained large quantities of spirochætes. As Uhlenhuth and I first showed, these are typical forms of syphilis induced experimentally in rabbits. This drug reacts most markedly on syphilitic indurations—the sclerotic, hard tissue, characteristic of primary specific disease.

When induced in rabbits, this tissue contains spirochætes in genuinely pure culture.[1] After one or a few injections (with small doses) the sclerotic tissue disappears altogether, no spirochætes can be discovered, the scrotal tissue has apparently again become normal, and the former deep ulcers are healing smoothly under good granulation formation. The specific reactions between the *S. pallida* and the arsenic and mercurial preparations, as I mentioned at the beginning, give us visible proof of the irritant nature of the spirochæte in human syphilis, as well as that of rabbits (Uhlenhuth and Mulzer).

After a few exploratory preliminary experiments on human subjects, which gave similar results to the successful ones on animals, Uhlenhuth recommended that

[1] It is a mistake if Hata, in the Ehrlich book "On the Chemotherapy of Spirilloses," asserts that we recommended syphiloma of the scrotum, which consists of loose myxomatous tissue and also contains a great quantity of spirochætes, for the purpose of testing chemotherapeutical experiments.

atoxylate of mercury should be employed for the therapy of syphilis. This new preparation was first used extensively in therapeutics by Miekley at the Lesser Clinique.

The administration of the drug was as follows: It was begun with doses of 0·05 gramme twice in the first week, and then continued with 0·1 gramme per week until a total amount of 0·5 gramme had been given (with women, 0·48 gramme).

The results obtained with these patients were well worthy of notice. Cases of syphilis in various stages were treated with atoxylate of mercury.

It was specially interesting to notice that frequently even after 0·05 gramme, or at most after 0·1 gramme, the papulous syphilides began to dissolve, the infiltrations especially disappearing very rapidly. "After the third injection, as a rule, all that was left of the papulous exanthemata was the pigment residue without any infiltration being clinically

evident," Miekley reports. He was further able to testify to a markedly favourable effect of hydrarg. atoxyl in malignant syphilis, and in the ulcerous and gummatous cutaneous processes of tertiary syphilis. The secondary effects—in some cases stomatitis and albuminuria—were very slight, and easily disappeared when the drug was stopped. According to a report of E. Lesser's in the *Charité Annales*, 1910, up to that time 127 cases had been treated in the Lesser Clinique with hydrarg. atoxyl. "The result on the whole was good, despite the relatively small dose, the phenomena generally retrogressed rapidly, and often disappeared after the first injection. The effect of hydrarg. atoxyl seemed to be specially favourable in galloping syphilis." Lesser states that out of these 127 cases, 16 relapses came under observation after the course of a few months. The result of the Wassermann reaction with 13 men was positive once and negative 12 times; with 17 women, 12 times positive and 5 times negative.

Blaschko also mentions good results he obtained with atoxylate of mercury ; only he gave larger doses than Lesser, as he extended them up to ten injections. The principal secondary effect Blaschko noticed was unusual pain during the injection, such as is not common to other mercurial preparations. He attributed this to the suspension of the preparation in olive oil.

Soon afterwards Fabry briefly recorded very good curative results in syphilis with atoxylate of mercury ; similar experiences were communicated by Lambkin. A more detailed account, completing Fabry's report, was given by Boethke in his inaugural dissertation.

Bergarth's results were less favourable, despite the fact that he injected larger doses than teachers had done previously. Atoxylate of mercury failed especially in his cases of syphilis gravis and maligna. According to the experience of this author, atoxylate of mercury, in the doses which were formerly administered in syphilitic processes, did

not appear to have the effect of salicylic acid mercury. Neither could this author detect any kind of increased secondary effects. Zieler is said to have observed that patients, who were first treated with atoxylate of mercury, and were then given grey oil, suffered less from the kidneys.

IV. HECTINE.

Mouneyrat called a " benzolsulphoneparaminophenylarsenate of sodium," which he produced synthetically, shortly " hectine." This body is supposed to be more active than the other arsenic preparations, and less toxic than atoxyl. The injurious optical secondary effects are also supposed to be absent. According to Balzer and Mouneyrat, hectine is specially effective in the secondary period of syphilis, in the tertiary stage with gummata and ulcers, and in very obstinate cases, which require prolonged treatment.

Hectine can be administered in a daily dose of 20 centigrammes, and continued for

about twenty to thirty days. From his experience, Hallopeau considers fifteen days' local treatment of the primary affection, combined with about thirty days' general treatment, is sufficient to cure syphilis. Certainly this must be commenced at once, if the presence of the *S. pallida* has been detected in any form of illness suspected of being a primary affection.

At the present time I am not aware that these statements of Hallopeau's have been further tested.

According to the communications of Neisser, hectine is said also to induce optical disturbances.

V. SOAMIN.

At the end of 1907, an atoxylic preparation, "soamin" (sodii *p*-aminophenylarsonas) was employed in England, which was supposed to be absolutely without toxic secondary effects. It was said to have a more constant arsenic content

than atoxyl, and was, therefore, capable of being administered with greater certainty than the inconstant atoxyl. So far, there are very few reports of the therapeutic application of this preparation in syphilis and other diseases; in reality, it is not distinguishable from atoxyl, and, like it, has given rise respectively to blindness and atrophy of the optic nerve in isolated cases (Lambkin, Pritchard, Johnston and others).

As we have seen, the correct chemical constitution of atoxyl was first recognised by Paul Ehrlich, together with its therapeutic application in trypanosome diseases. Starting from this, the purposeful and indefatigable effort of this researcher was to prevent "the uncertain and doubtful action of atoxyl in trypanosome diseases by means of appropriate alterations of the arsenic-fast residue," and so "procure a reliable arsenic drug of which there could be no doubt." In other words, Ehrlich set himself the task of finding curative substances for the treatment of trypanosome diseases

in which the *parasitotropic* groups—*i.e.*, those which destroy the parasites—are increased, while, on the other hand, the *organotropic*, which have an injurious effect on the vital organs, are diminished as much as possible.

The toxic organotropic action of atoxyl and of arsacetin was attributed by Ehrlich to the fact that these preparations contain a quinquevalent arsenical residue. By continuously reducing this substance, Ehrlich was able to form the arsenic combination in such a way that a trivalent arsenic residue was substituted, and therefore, in his opinion, this new preparation must be less toxic and distinctly parasitotropic in its action.

In this way, by means of chemical synthesis, Ehrlich, after numerous experiments, succeeded in obtaining

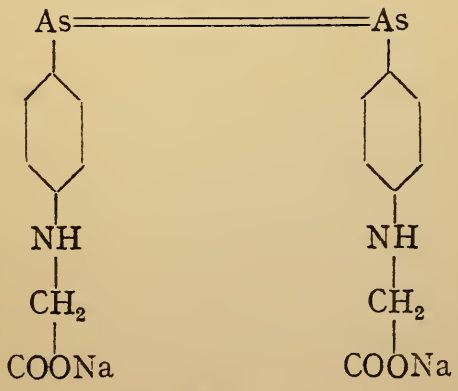
VI. ARSENOPHENYLGLYCIN,

a preparation, which appeared to possess in a high degree the characteristics Ehrlich had endeavoured to obtain, by means of

comprehensive experimental tests. In consequence of the strong parasitotropic action of this preparation, Ehrlich hoped to entirely destroy the parasites in experimentally induced trypanosome diseases, by means of a single adequate application (*dosis efficiens tolerata*), and to a certain extent to " sterilise " the organism.

Ehrlich describes this new therapeutic procedure in the treatment of diseases of this kind, as *Therapia sterilisans magna*, in contradistinction to the usual gradual treatment with smaller doses, the administration of which was repeated at shorter intervals.

The chemical constitution formula of arsenophenylglycin is as follows :



The preparation is represented by a yellow powder easily soluble in water. It can be preserved for some time in hermetically sealed vacuum tubes, whereas, when it comes in contact with the atmosphere, it gradually discolours, becomes a reddish-brown, and oxidises into a more toxic product.

Uhlenhuth reported at the Colonial Congress (October 6, 1910) that, from the reports of Ulrich and Scherschmidt in Africa, it appeared that, in treating sleeping sickness with arsenophenylglycin, injurious effects had been observed in numerous cases, which were partly of a threatening nature. These consisted in cutaneous eruptions, paralyses, emaciation, and in some cases of epileptic attacks. The cutaneous eruptions, which covered the entire body, were very unpleasant, and gave rise to the formation of vesicles and necrosis. Uhlenhuth stated that Scherschmidt reported as specially unfavourable the fact that, even after a single administration of 1 to 2 grammes of

arsenophenylglycin in quite fresh cases, emaciation and prostration were observed, and even death in some, a few days after the injection.

Von Raven, who also observed toxic secondary effects, specially gave a warning against the employment of repeated small doses, as these are followed by hyperæsthesia and phenomena of intoxication. For the rest, his results in the treatment of sleeping sickness were more favourable in Togo than they were in East Africa; obviously, also, the course of this disease is much slighter in Togo.

On the recommendation of Ehrlich, Alt for the first time administered this preparation to patients suffering from mental disease, idiotcy, and epilepsy with a syphilitic foundation. He administered this preparation in a single concentrated dose. In accordance with Ehrlich's *therapia magna sterilisans*, instead of the customary gradual treatment which had been employed previously, Alt firmly believed that he would

be able to testify to the specific action of arsenophenylglycin in these diseases. Conjointly with a rapid and durable improvement in a great number of cases, he perceived the disappearance, or at least the diminution, of the positive result of the Wassermann reaction.

Further experiments of this kind, especially in florid or tertiary syphilis, have not been undertaken with arsenophenylglycin, or have not been published.

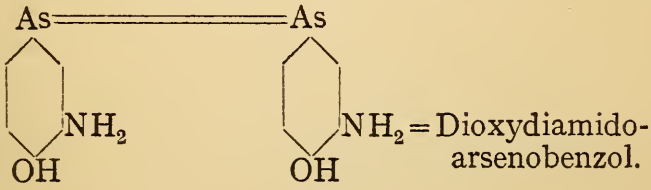
On the occasion of a post-graduate lecture, delivered during the winter term of 1909-10, Ehrlich first reported that he had found a new preparation, which in its chemotherapeutical action surpassed arsenophenylglycin.

VII. DIOXYDIAMIDOARSENOBENZOL (EHRLICH-HATA, "606"),

like all the arsenic preparations already mentioned, belongs to the group of aromatic arsenic combinations. Ehrlich sent it to Professor Alt in September,

1909, to be tested clinically. The extensive experiments on animals of his collaborator Hata had already proved its extraordinary efficacy in relapsing fever of mice and rats and in syphilis of rabbits.

The Ehrlich-Hata preparation, "606," as it is now briefly called, has been produced by Dr. Bertheim, who has for years worked with Ehrlich. Its formula is as follows:



= Dioxydiamido-arsenobenzol.

In Ehrlich's opinion, this must be regarded as the genuine destructive agent of the arsenic residue, while the side-groupings cause the primary anchoring of the parasites.

1. Experiments on Animals.

Analogously with the experimental tests of atoxyl made by Uhlenhuth and his collaborators, Ehrlich and his co-worker Hata studied the effect of the new prepara-

tion on the spirilla of relapsing fever, spirillosis of fowls, and syphilis of rabbits, by means of observations on animals. Thus, from a large series of chemical preparations, Hata succeeded in finding the maximum spirillicide action in two substances produced by Bertheim—namely, in arsenophenylglycin, discussed on pp. 40 to 44, and in the one just mentioned, "Ehrlich-Hata '606.'" Mice, infected with the spirilla of the relapsing fever, were cured by a single dose, which contained a third of the *dosis maxima tolerata*. According to the statements of Ehrlich, Hata obtained most excellent results with this preparation in spirillosis of fowls, 1·5 milligrammes per kilogramme of the animal's weight of this combination being sufficient to effect a cure. When transferred to man, this dose would only correspond to one of $\frac{1}{10}$ gramme. When a dose of arsenobenzol is injected intramuscularly into fowls, infection only takes effect at the end of thirty to forty days, but after intravenous injection it

does so after three or four days. Hata was also able to obtain most brilliant results in syphilis of rabbits. The cure of very large chancres could be effected by means of a single dose. On the day following the injection, the spirilla, which before had been present in large quantities, had disappeared, and this was followed in the course of two to three weeks by complete cure with a smooth cicatrix. Tomasczewski was also able to testify to a good effect of arseno-benzol on the products of experimental syphilis in rabbits. At latest, thirty-six hours after the injection, and at the earliest, twelve hours after, the spirochætes had disappeared. The symptoms began to retrogress after ten to fourteen days.

Neisser's curative results were less favourable with apes in which syphilis had been experimentally induced. Out of twelve syphilitic apes, which had been treated intramuscularly with 0·025 per kilogramme weight, and intravenously with 0·015 per kilogramme, up to the time of publication

only three had been definitely cured ; two were probably cured, and the remaining seven at the present time must be regarded as uncured. Two apes were given an intramuscular injection of 0·025 per kilogramme eleven days after inoculation. Here the primary affection set in much later, and to a much slighter extent than in the control animals, which had been inoculated simultaneously, but not injected.

Uhlenhuth and I, in the observations we made on animals in this direction, could not determine any special difference between the effect of arsenobenzol, atoxyl, and atoxylate of mercury respectively. With the last preparation especially, the larger doses had precisely the same effect as arsenobenzol on the spirochætes of spirillosis of fowls, and syphilis of rabbits, as well as on their clinical manifestation. We were, however, able to prove the prophylactic power of an injection of arsenobenzol against infection with

spirillosis of fowls during a period extending over twenty-five days. Observations on animals have proved the superiority of "606" to other preparations in relapsing fever.

If we again glance at the path which led Ehrlich and Hata to the discovery of this new syphilitic drug, we see that the starting-point was atoxyl, the spirillicide and specific anti-syphilitic action of which had been experimentally proved by Uhlenhuth. There can, therefore, be no doubt that the experimental foundation of the modern arsenic therapy of spirilloses was laid by Uhlenhuth and his co-workers. Uhlenhuth himself, when the toxic secondary effects of atoxyl became known, was one of the first to issue a warning against its general employment in the treatment of syphilis. In the firm conviction, however, that the organic arsenic compounds were called upon to play a great part in the therapy of syphilis, he, as well as Ehrlich, endeavoured to discover new, less toxic, modifications of atoxyl.

The practitioner who wishes to successfully employ the new remedy "606" must be accurately instructed as to its action and secondary effects, mode of application and height of dosage. In the following pages, therefore, I shall attempt to summarise the most important points from the literature on the subject, which is already considerable.

2. Suspension of Solutions which are Prepared Ready for Use.

The preparation "Ehrlich-Hata '606'" is a sulphur-yellow powder, hermetically sealed in a vacuum tube in correct doses.[1] It dissolves in hot water as double hydrochloride salt, but Ehrlich states, and the experience of Alt, Schreiber, and Hoppe show, that it should not be injected in this condition, as it is liable to become toxic. By the addition of solution of caustic soda,

[1] According to the most recent communications, it has been placed on the market under the name "Salvarsan," in doses of 0·6 gramme in hermetically sealed glass tubes.

it can be transposed into mono- or di-sodium compound and dissolved. This solution, however, is not very stable, and must always be freshly prepared.

Now, during the time required for testing this preparation clinically, the production of solutions which are ready for use has undergone the most varied changes and modifications. As no definite decision has yet been arrived at as to their relative value, I will, as far as possible, give all the methods known up to the present time.

(*a*) ALKALINE SOLUTIONS.

1. IVERSEN'S METHOD.—Iversen first injected a 0·5 to 2 per cent. aqueous solution of the preparation "606" under the shoulder-blade or intramuscularly. He gave the following prescription for intravenous injection :

"For this purpose I dissolve the substance as for intramuscular application, in about 15 c.c. of aq. dest., add normal solution of caustic soda, drop by drop,

until the sediment is dissolved, then neutralise the excess of caustic soda solution, drop by drop, with 1 per cent. acetic acid (about 2 c.c. of 1 per cent. solution to 0·3 arsenobenzol), pour this to half a litre of physiological salt solution heated to 40°; shake the bottle (infusion apparatus) moderately, and inject by means of a hollow needle direct into the cubital vein."

2. ALT'S METHOD.—The method originally employed by Alt for the suspension of solutions ready for intramuscular injections of arsenobenzol is the following:

"A single dose, 0·3 and about 10 c.c. sterile water, is poured into a low measuring glass of about 50 c.c. content and shaken. Sterile N solution of caustic soda is added, until only a slight residue of the substance remains undissolved; for this 2·0 to 2·3 c.c. N solution of caustic soda is necessary. The cylinder is now filled with sterile water up to the stroke 20 c.c., sometimes after having added a sterile anæsthetic. With

a syringe containing 10 c.c. of the solution the injection is made deep into the right and left gluteal muscles, while slowly pressing the knob."

Alt still adheres to the plain alkaline solution, which is prepared solely by the careful addition of normal solution of caustic soda. After exact and comprehensive experiments on animals and man, it has been proved to be the most effective and simultaneously the least injurious. Alt's recent instructions for the rapid suspension of a good alkaline solution are as follows :

" Put about thirty glass beads of medium size (similar to those used for filling pen-holders) into a slender graduated glass cylinder of about 100 c.c. content, with a narrow neck and glass stopper. Add 10 c.c. of distilled water, and then the substance. Shake energetically, and the whole will dissolve quite clearly. To every 0·1 gramme of substance add about 0·5 c.c. of normal solution of caustic soda, and then shake energetically for about half a minute.

A perfectly wine-clear, weakly alkaline solution has now been obtained, which can be further diluted at will by the addition of distilled water. As the preparation is not always equally soluble, a slightly greater or smaller quantity of solution of caustic soda may be necessary, in order to obtain the wine-clear suspension. This can be produced in the shortest time without any preliminary preparation, and is easily sterilised; it has the further advantage that only a small quantity of solution of caustic soda is required, and consequently less pain is caused."

3. WECHSELMANN'S METHOD.—The following is Wechselmann's report of this:

"At first I dissolved the dose of di-hydrochloride of diamidoarsenobenzol, which was hermetically sealed in a vacuum tube, with a little methyl alcohol or glycol; to this about 10 c.c. of distilled water was added, then 1 to 2 c.c. $\frac{N}{10}$ normal solution of caustic soda; finally it was filled up to 25 c.c. with water, and this strong

acid solution injected. Later we added sufficient $\frac{N}{10}$ solution of caustic soda to give a slight trace of opalescence, when the monohydrochloride was formed. We also employed the drug dissolved only in water or in a little fluid as above. We observed little difference here with regard to the pain."

4. EHRLICH'S METHOD. — Instructions, which Ehrlich himself gives for the suspension of clear solutions of his preparation, run as follows (according to Schreiber and Hoppe) :

Solution of "606" 1 : 100 (*Intramuscular Injection*).—"Dissolve 0·6 gramme of the substance in 3 c.c. glycol while stirring well with a glass rod ; the addition of a few drops of water will assist the solution. Now add 12 c.c. water, shake and dilute with 10·3 c.c. $\frac{N}{5}$ – NaOH in one portion. On shaking, a clear solution is formed, which can be made up to 60 c.c. with water.

"It is advisable that this entire process should be carried out in a graduated cylinder."

Attenuated Solutions (*for Intravenous Injections*).—Solution A : 0·6 gramme of the substance, 0·3 to 0·5 c.c. methyl alcohol, or 3 c.c. glycol.

Solution B : 240 or more c.c. physiological NaOH solution, 10·3 c.c. $\frac{N}{5}$ – NaOH.

While shaking well, solution A is poured into solution B.

5. The Method of Schreiber and Hoppe.—" A single dose 0·6 to 0·7 gramme and 0·5 methyl alcohol are placed in a mixing cylinder of 150 c.c. content. As soon as the substance is moistened, about 10 c.c. of sterile water is added and thoroughly shaken. Then add sufficient sterile $\frac{N}{1}$ – NaOH solution to almost entirely dissolve the substance, so that after prolonged vigorous shaking only the slightest residue remains undissolved ; for this about $3\frac{1}{2}$ to 4 c.c. of $\frac{N}{1}$ – NaOH solution is required. Fill up to 60 c.c., and of this solution inject 30 c.c. through a fine cannula, under the most regular pressure possible, into the right gluteal muscle, and 30 c.c. into the left."

For intravenous injection, the authors first of all used this solution without diluting it, but later they cautioned operators against the employment of a concentrated solution. The exact description of their suspension for intravenous injection is as follows :

" Into a graduated measuring cylinder of 250 c.c. capacity (with a glass stopper and narrow neck) put about 10 to 20 c.c. of sterile water. Then add the substance (0·3 gramme for women and 0·4 for men), and shake thoroughly until a clear solution is obtained. The addition of methyl alcohol is now no longer necessary, as the preparation in this present form (" Hyperideal 606 ") dissolves easily in water. This solution is brought up to 100 c.c. with sterile water or physiological common salt solution. Then per 0·1 of the substance, add about 0·7 c.c. of normal NaOH solution, and shake well until the existing residue is thoroughly dissolved. If after a good shaking the solution is still opaque, a few drops of normal

NaOH are carefully added until the solution is perfectly clear, and then this is filled up to 200 c.c. (of course, instead of 200 c.c., it is possible to select either 150 c.c. or 250 c.c.). For solution as well as for filling up, it is best to use warm water."

(*b*) NEUTRAL EMULSIONS.

1. METHOD OF LEONOR MICHAELIS.—" A wide measuring cylinder of 50 c.c. capacity is filled with 25 c.c. of water, which has been boiled a short time before, and is still quite hot. Then add 0·6 gramme of the substance, and dissolve by rubbing and stirring backwards and forwards with a glass rod. If the whole substance has been dissolved without leaving any residue, then 6 c.c. of normal (not $\frac{N}{10}$) NaOH is added, and it is stirred until the precipitation which has resulted is entirely dissolved. Then 3 drops of a $\frac{1}{2}$ per cent. alcoholic solution of phenolphthaleïn are added, and normal acetic acid, while stirring all the time, until the reaction is neutral—*i.e.*, until the

phenolphthaleïn has lost its colour. The neutral suspension is now formed, the appearance of which is bright yellow. In order to definitely prevent the rise of an alkaline reaction, normal NaOH is again added, drop by drop, until the phenolphthaleïn appears to be tinged very slightly red. This fluid is poured off into a flat sterile shell, and injected subcutaneously into the back."

Later, Michaelis deviated somewhat from the above-described method, in that he moistened the solid preparation with 1 c.c. absolute ethyl alcohol in the measuring cylinder, and pricked through with the glass rod until the preparation was thoroughly wetted everywhere with the alcohol. The hot water was then poured on, and solution rapidly obtained by simply stirring with the glass rod.

2. Method of Wechselmann and Lange.—Almost simultaneously with L. Michaelis, Wechselmann devised the following methods of suspension :

(*a*) "606" is dissolved as before, a few drops of phenolphthaleïn solution, as an indicator, and $\frac{N}{10}$ NaOH carefully added, until a fine yellow powder is again precipitated. This weakly acid or neutral suspension of 25 to 30 c.c. is injected intramuscularly or subcutaneously into the gluteal region.

(*b*) After rubbing "606" in a mortar, it is dissolved in 1 to 2 c.c. of commercial NaOH solution. By adding glacial acetic acid drop by drop, a fine yellow sediment is precipitated, which can be sterilely suspended with 1 to 2 c.c. of distilled water, and then neutralised by the addition of $\frac{N}{10}$ NaOH or 1 per cent. acetic acid most accurately with litmus-paper. The absence of pain depends upon the accuracy. The suspension is drawn into the syringe, and injected slowly subcutaneously under the shoulder-blade, at a place which has been previously disinfected.

3. Spiethoff's Method.—By modifying the instructions laid down by Michaelis

for the preparation of an emulsion, it is possible, according to Spiethoff, to reduce the amount of the injection when using 0·6 gramme arsenobenzol from 9 to 10 c.c. 0·6 gramme of the substance is placed in a large centrifugal glass. To this is added a few c.c. of hot sterile physiological saline solution. It is shaken thoroughly and broken up with the glass pestle, with the addition of further hot physiological saline solution. For the preparation of a complete suspension, 8 c.c. of saline solution is adequate. Then add 2 drops of phenolphthaleïn and about 3 drops of concentrated NaOH solution. A few rough reddish flakes will form, which on stirring become more and more numerous and finer, until finally a pulpy mass appears, which becomes a fine emulsion with further stirring and occasionally warming the glass in hot water. Add a few drops of concentrated NaOH until a light reddish colour appears, when a few drops of strong acetic acid solution must be added, till the red

colour again disappears. The excess of alkali is again removed at the bedside immediately before the injection itself, by means of a few drops of normal NaOH. Any residue left in the glass is washed out by 1 c.c. of sterile distilled water. In this way, one can reduce the volume required for the injection of 0·6 gramme to about 9 or 10 c.c., which has the result of diminishing the pain."

4. Method of Blaschko.—According to Blaschko, one should only add just sufficient soda to again precipitate the base out of the salt. "The amount can be determined just as well by calculation as by rubbing. For 0·5 gramme of the salt it requires 0·45 gramme = 0·36 of a 20 per cent. NaOH; for 0·45 gramme of the preparation, 0·41 gramme = 0·33 c.c. NaOH; for 0·06 gramme of the precipitation, 0·55 gramme = 0·45 solution of caustic soda. If the soda is added carefully, and a little sterile water, it is possible to at once produce a neutral suspension, or at most one

that requires one or two drops of weak acetic acid or, better still, hydrochloric acid. If the emulsion is then filled up to 8 or 9 c.c., we have a physiological common salt solution of 0·82 to 0·75 per cent. which contains a suspension of the base. It is sufficient, however, if it is filled up to 5 c.c., for a saline solution of 1·3 per cent. is not so hypertonic that it is painful in any way."

5. Method of H. Citron and the Author.—Starting from the fact that all manipulations for the suspension of ready-prepared solutions of arsenobenzol already described, are associated with certain details which may appear undesirable for the busy medical man, and more especially because the possibility of chemical changes in the very subtle preparation may render sterile work difficult, we have devised the follow-method :

" The necessary amount of Hata powder for injection is shaken into a sterile Record syringe of 15 c.c. capacity, which is closed

with a cone at one end of the cannula, and moistened with a few drops of alcohol. The stopper has been previously removed. The syringe is filled up to mark 5 with hot distilled water, the stopper readjusted, the ligature ring put on, and thoroughly shaken. A clear golden-yellow solution results. The stopper is now taken out again, and 40 drops of a 10 per cent. suspension of calcium carbonate in physiological NaCl solution added slowly while shaking continuously. By removing the cone, a little carbonic acid is allowed to escape from time to time. A creamy, extremely fine emulsion is formed, somewhat of the appearance and consistency of egg brandy. The addition of 40 drops of the 10 per cent. calcium carbonate suspension is found from experience to be sufficient for the complete precipitation of the base. As we have been able to convince ourselves by centrifugalisation, the fluid decanted is entirely without colour. In contradistinction to the old methods of

suspension, a small excess of the precipitate is without importance. The resulting amount injected consists of about 5 to 6·5 c.c., but we have no doubt that one could make smaller quantities suffice. After the precipitation is finished, the stopper is screwed on, and a cannula appended, which is not too fine. We select the upper external quadrant of the gluteal region exclusively as the seat of injection."

The 10 per cent. calcium carbonate suspension is sterilised by placing it in a drop-glass, which is closed by a wadding plug, and sterilised in the autoclave.

(*c*) KROMAYER'S PARAFFIN EMULSION.

Kromayer employs the preparation "606" in the form in which it is sent—viz., as a dichlorate—by making an emulsion with paraffin, analogous to a mercurial paraffin emulsion, which he prepares as follows :

"A certain amount of Ehrlich's '606' —for example, 3 grammes—is mixed with

a little liquid paraffin in a sterile mortar, and is carefully rubbed very fine, while more paraffin is gradually added. It is put in a sterile bottle, of 50 c.c. capacity, with a glass stopper, and is filled up to 30 c.c., so that each c.c. of the emulsion contains 0·1 gramme of Ehrlich's "606." It must be shaken before using until all sediment has disappeared and be protected from light. On account of the fear of the cannulas becoming blocked, they should be selected somewhat stronger than those used for Hg salicylic injections, and it is best to keep them in Petri saucers, covered with liquid paraffin. In this case, it is no more necessary to sterilise the cannula each time before using than it is in Hg injections. The injections with "606" are made exactly in the same way as the former, and ambulant patients can also be treated."

These are the principal methods which have been proposed and clinically tested by many authors up to the present for the purpose of making the new Ehrlich

preparation "606" ready for use. Still further small alterations of these methods have been proposed by various authors. Thus, Loeb adds 1 to 3 c.c. 1 per cent. acetic acid to the alkaline solution, as, in his experience, the pain of the alkaline solution is thus considerably diminished. The fact that this solution is less painful is obviously due to the solution of caustic soda being partially neutralised, which is evidenced by the gelatinous-nuclear precipitation. Saalfeld, Fränkel, and Grouven only add 1 to 1½ c.c. of $\frac{N}{10}$ NaOH solution to the hydrochloric solution, which certainly does not intrinsically influence the acid reaction. Junkermann does not employ normal NaOH solution for the purpose of alkalisation, but, instead, the strong official 15 per cent. solution of caustic soda.

Passini prepares a neutral or very weakly acid emulsion by means of NaOH and glacial vinegar in the usual way, and then rubs this mass carefully with a mixture of

adeps lanæ anhydricum and vaseline oil in equal parts.

Nearly all these methods for the preparation of ready-to-use solutions have been found to be equally good in animal experiment and by the sick-bed. According to Hata's observations on animals, the preparation is quickly secreted when injected intravenously, whereas, when administered subcutaneously and intramuscularly, it remains deposited in the body a long time, and develops a prolonged action. With regard to the rapidity of the disappearance of the spirochætes from the syphilitic diseased tissue, Spiethoff was unable to discern any difference between the effect of the solution and that of the emulsion. Nevertheless, from the researches of various authors (A. Neisser and others), the action of neutral emulsions appears to be slower, but more persistent. Alt, Schreiber, Hoppe, and others, attributed a more rapid, but at the same time less lasting, effect to the intravenous incorpora-

tion of the preparation. For this reason, Iversen combined this mode of application with intramuscular injection — a method which is also recommended by Ehrlich—in such a way that he first injected a little over half (0·4 to 0·5 gramme) the dose of arsenobenzol intravenously, and at the end of forty-eight hours injected the remainder (0·3 to 0·4 gramme) intramuscularly. Wechselmann, L. Michaelis, Herxheimer, Sieskind, and others, as a rule prefer to make a subcutaneous injection in the interscapular region or between the shoulder-blades, whereas the majority of teachers like an intramuscular injection deep in the gluteal region.

In the experience of Alt, the incorporation of acid solutions, as already mentioned, is apparently not innocuous, and even in small doses they may have an unfavourable effect upon the heart's action. Even Ehrlich himself, as well as Junkermann and others, suspects that the preparation as dichlorohydrate may have an irri-

tant and occasionally a toxic action on the tissue. This suspicion would also apply to Kromayer's paraffin emulsion, in which, further, the bad absorptive capacity must be taken into consideration. If these suspicions, however, are got rid of, as Kromayer has reported, after extensive clinical application and observation, then the paraffin or vaseline oil emulsion he recommends may possibly be used for injection and for the practical employment of the preparation. Meirowsky, however, could not confirm Kromayer's assertions that this method of injection only caused slight pain. Further, he fears the possibility of the great quantity of paraffin injected favouring embolism, a circumstance which he verified in an observation of his own. Similarly, the method which Citron and I worked out should be recommended for medical practice, as the ready-prepared solution, which guarantees the smallest imaginable chemical changes, is absolutely sterile and perfectly neutral, and conse-

quently fairly painless in itself. The momentary action of this emulsion is apparently like that of others, but whether the conditions of absorption are also the same can only be determined after a larger number of cases have been treated with it. Still, one may assume that these would certainly not be more unfavourable than with Kromayer's paraffin emulsion, described above.

As regards the

3. Technique of Injection,

the following points are worthy of observation, from experience gained up to the present :

(*a*) intramuscular injection.

This is made in the muscles of the gluteal region, as in the intramuscular application of mercurial preparations. It is best for the patient to lie on his abdomen when on the operating-table. The gluteal region is disinfected in the usual way

(according to Fürbringer, with tincture of iodine or iodine benzine), and the puncture is made in the upper external quadrant. In order to remain as far as possible from the sciatic nerve, and so avoid more intense pain, Junkermann advises that the injection should be made at the height of the connecting line of the spinæ iliacæ anteriores superiores, and the cannula inserted slowly into the gluteal region in a sagittal direction, and as far laterally as possible. This is done in order to avoid piercing the larger vessels of the gluteal region. When employing solutions of the preparation, the injection can follow at once with the usual cannula. Air bubbles must obviously be prevented. When injecting emulsions, it is better to employ somewhat larger needles, and, as in insoluble mercurial preparations, remove them from the syringe before the injection, in order to convince oneself that no vessel has been pierced (Lesser's handle should be used). The injection itself is always made extremely

slowly, in order to avoid tearing the tissue as much as possible (Kromayer). If neutral emulsions are injected, then the relatively small amount required can be syringed into one side of the gluteal region. It is best to select the side on which the patient as a rule does not sleep (Spiethoff and others). It is advisable that the patient should remain lying on his abdomen for a little time longer. After the seat of injection has been fastened with a sterile plug, covered with a wide piece of sticking-plaster, the region should be vigorously massaged for about half an hour. Vibratory massage may also be applied as after a mercurial injection.

(*b*) SUBCUTANEOUS INJECTION.

This is recommended chiefly by Wechselmann and Lange, L. Michaelis and Kromayer. The patient, according to L. Michaelis, is placed in a completely perpendicular position, and the cannula inserted in the region between the shoulder-

blades. "After emptying the syringe, the dispersion of the injected mass follows, which is the most important part of the entire procedure. The patient is seated transversely on the bed in an upright position, and then, by means of careful massage, the ball of fluid is spread over the greatest possible surface, so that no further protuberances are visible. Then a moist dressing is applied to the back, and the patient put to bed." Michaelis now makes the injections somewhat deeper into the dorsal muscles; he no longer injects quite at the back, but instead laterally and under the thorax.

Wechselmann and his collaborators (Lange and Sieskind) make the subcutaneous injection in the right interscapular region.

Blaschko injects into the subcutaneous tissue of the nates, and considers that in this way, with hardly perceptible infiltration, all functional disturbances are avoided. Moreover, in order that the conditions of absorption may be more favourable, he

spreads the dose injected over various places in smaller quantities.

Larger "Record" syringes are most suitable for both intravenous and intramuscular injections.

(*c*) INTRAVENOUS INJECTION.

An accurate description of the intravenous injection is given by E. Schreiber, which I will quote here in his own words :

"The solution (see p. 57) is then put into a sterile measuring glass, from which it can be easily sucked up with the syringe.

"The syringe we now employ is a simple Lüer one. The cannula is bayonet-shaped, bent, and has a lateral attachment-piece with a three-way stopcock, so that not only can the fluid be drawn up, but after the tap is turned it can be injected into the vein. Further, the cannula has also a small plate bent at right angles at the first joint, for the purpose of fixing the syringe better. It is now made to screw off, so that it can be easily changed.

"It is very important that the cannula should rest properly in the vein, and that on puncturing no further injury should be done, which may easily happen with the cannula if the syringe is too long; therefore, I only have the syringe obtusely bevelled. In order to be absolutely certain, we use a short handle, which I can thoroughly recommend, especially to those who are making the injection for the first time.

"We first fill the syringe with physiological saline solution; then, with the tap open, pierce into the vein, and while the ligature is still in position, make the injection, only syringing in the saline solution after blood has poured in distinctly. Now, if the cannula does not rest completely in the vein, or this has been injured in any way by the puncture, infiltration will at once result on injecting the saline solution. If this occurs, we withdraw the cannula from the vein and try to find another better position. In every

case care must be taken to prevent any of the solution getting under the skin in the subsequent injection, because this causes unpleasant infiltrations. In some instances these are very painful and persist for weeks, although later, without exception, they recover well. Consequently, we, as a rule, select a vein which lies outside the elbow-joint, so that, in the event of such infiltrations, movement is not interfered with. Similarly, when the whole of the solution has been injected, we again syringe out the vein with saline solution, in order to avoid any irritant action upon the lower parts of the vein. If, during the injection of the solution, the cannula should be withdrawn from the vein, or have injured it, then a protuberance will at once appear on injecting, and the patient will at the same moment complain of a burning feeling. The syringe should be at once withdrawn, the ligature replaced, and a reasonable amount of bleeding allowed, because we have found that this is the best

way to avoid infiltration. If technically the injection has been a complete success, the patient will have no pain apart from the small puncture."

Besides the intravenous injections with a cannula provided with a tap and syringe, described by Schreiber, an infusion into the vein through rubber tubing and a funnel (Weintraub) has been practised successfully. Assmy has brought out a small set of instruments for this purpose, with which it is possible to give an intravenous injection without any assistance; this could hardly be done with the Schreiber method. Another advantage of the Assmy set of instruments over those of Schreiber is their cheapness and greater durability. On a stand about 1 millimetre high (volumetric stand) two funnels are fastened for the reception of the "606" and saline solutions respectively; two tubes start from them. These are united by a two-way stopcock (Posner's catheter tap); on its attachment a thin

rubber tubing, about 12 c.c. long, is fixed, which has a metal cone at the end for the reception of the cannula. The latter corresponds in form to the Strauss cannula, as it is generally applied for the removal of blood for the Wassermann reaction, only, naturally, it is thinner, shorter, and its end is bevelled off obtusely in the same way as the Schreiber stopcock cannula.

The arrangement of the rubber tubing between the cannula and stopcock makes it possible to carry out all possible manipulations with the latter without the cannula, which is resting in the vein, participating in the movements thus caused. This is a great advantage, as with the Schreiber method the danger of injuring the walls of a vein naturally persists during the entire interference. In consequence of the long lever which is formed by the syringe and the stopcock cannula, even the slightest movements, such as cannot possibly be avoided in the individual phases of the injection, are unpleasantly perceived in

an exaggerated form on the syringe cannula.

Assmy, who has carried out numerous intravenous manipulations in both ways, states that the infusion method is incomparably easier, and demands less expertness than the Schreiber injection technique.

Whereas Ehrlich, even in his book[1] (p. 152), recommended the intramuscular injection, and attributed a more persistent and intense action to it, in a circular letter of October 25, 1910, he advises that, in the further treatment of syphilis with his preparation, the *intravenous* injection should be employed whenever possible.

From the standpoint of guaranteeing a permanent result, Ehrlich now considers that the following are most effective :

1. The *intravenous* injection of alkaline highly attenuated solution.

2. The *intramuscular* injection of alkaline solution.

[1] "The Experimental Chemotherapy of Spirilloses" (Rebman Limited, 1911).

3. The strongly irritant acid solutions (mono-dichlorhydrate).

4. Finally, the so-called neutral emulsions (intramuscularly and subcutaneously).

4. Direct Local Secondary Effects of the Injection.

Whereas with correct technique no local secondary effects are attached to the intravenous injection, various local disturbances are evident with the intramuscular and subcutaneous application of the Ehrlich preparation. These are induced partly by the kind of solution, partly as the result of pressure of the greater or smaller quantity of the substance injected.

These local secondary effects are most intense and unpleasant with the injection of alkaline solutions, especially when larger quantities of fluid are employed, as was done almost always at the beginning.

These secondary effects appear first of all as pain in the buttocks. When alkaline

solutions are employed, the pain generally sets in during the injection, and increases in intensity within the following hours. Consequently, it is advised that the injection should be made in the morning, so as to interfere as little as possible with the patient's night's rest.

As already mentioned, the pain increases the following day. It is of a boring character, something like toothache, and, further, there is generally a feeling of pressure in the gluteal region, which meanwhile has become as hard as board, infiltrated, and diffusely swollen. This pain affects the patients most when walking, sitting, and lying down. Very often the tension makes it almost impossible to move the thigh. Moreover, the pain may be localised in the region of the os coccyx (Spatz). With the intramuscular injection of neutral emulsions, the pain as a rule only begins on the following day, attaining its highest point on the second or third day, during which time, under symptoms

of regular fever, a fairly circumscript, hard infiltration has been formed, the size of which varies with the larger or smaller amount of emulsion which has been injected. The sensation of pressure here is markedly less severe than with alkaline solutions, and the pain is no longer felt as a boring one, but, instead, as a dull, painful pressure. Latterly, various authors have observed severe necrosis extending up to the bone at the seat of puncture, in intramuscular as well as subcutaneous administration. Thus Dreuw in two cases observed necrosis of the gluteal muscles, almost the size of a small fist, and in another case there were two necroses the size of hazel nuts in the back. Bayet saw eight severe gangrenous affections in eight patients, which were in part connected with necrosis of the bone at the seat of injection.

The greater percentage of patients are supposed to tolerate the injection excellently and without reaction in cases of subcutaneous application (Sieskind, L

Michaelis, Kromayer, and others). According to Sieskind, however, with the subcutaneous method also reaction phenomena were observed in about 10 per cent. of the cases. The occasional infiltration only sets in here after three or four days. It was frequently possible to determine a fluctuation in the infiltration, which, however, in Sieskind's opinion, owed its origin to a serous fluid, as was proved by the exploratory puncture. Out of 275 cases, Sieskind only five times observed genuine suppuration. The pus was sterile in all five cases. "Quite small necroses at the seat of puncture are not rare, which is not surprising when one considers the inflammatory and necrotic effect of arsenic preparations. The small necroses healed by granulation." Two patients had necroses as large as two-shilling pieces extending to the muscle. According to Sieskind's observations, necrosis always sets in if any of the preparation has been left behind in the puncture canal.

The very unpleasant irritation of the sciatic nerve may be regarded as a direct effect of this infiltration, and this may make itself evident in neuralgic pains, which extend right down to the calf of the leg. In cases in which there is a pronounced inclination to sciatic troubles, or in which sciatica exists, an intramuscular injection should be avoided, as this pain, as I myself saw in one case, is increased thereby, or may again break out.

In order to prevent—or at least diminish—the pain of injection, which under some circumstances may be very considerable, not only with neurasthenics, but also with healthy, robust persons, it was at first recommended from various sources that an anæsthetic should be added to the injection fluid. Thus, Alt advised the addition of an ampulla of eusemin. Wechselmann renders the seat of injection anæsthetic by means of a preliminary injection of 0·02 novocain; others, again, add cocaine, alypin, or morphia. But the transitory

nature of all these precautions made them no protection against subsequent pain. Apparently the best prophylactic, as already mentioned, is to neutralise the liquid as accurately as possible, and to massage the seat of injection immediately after the operation. Good service is rendered by permanent bandages moistened with acetic acid, Fuller's earth, or spirit, as a protection against the pain of pressure. Further, the usual narcotics, such as opium, are best here as suppositories and hypnotics.

5. Effect of Arsenobenzol on the Organism in General.

As far as the influence of the preparation concerns assimilation, Hoppe was able to testify to a favourable effect on the lecithin assimilation. With most patients, a few days after the injection fairly considerable leucocytosis sets in. A. Neisser also saw very pronounced hyperleucocytosis (up to

38,000), the dissonance of which occurred slowly. Brändle and Clingestein obtained almost the same result (up to 15,000), whereas in isolated cases Lange only saw a slight increase of leucocytes.

Klausner and Bardachzi noticed great variations in the number of red blood-corpuscles after an injection of arseno-benzol, generally during the first eight to twelve hours, accompanied by the appearance of urobilinuria; the latter again disappeared usually after twenty-four hours.

Alt states that in intravenous injection the secretion of arsenic is almost completed at the end of two days, and on the third day only traces are found. "Within this period, one can detect nearly the whole of the arsenic in the fæces and urine, apart from small quantities which are lost through perspiration, the skin, hair, etc." In intramuscular injections the secretion of arsenic lasts at least twelve to thirteen days (Treupel and others), whereas in intravenous injections it has already ter-

minated at the end of four days (Hoppe). A methæmoglobin formation, such as might be expected in an intravenous injection, Heuber says does not take place, even with the strongest concentration.

W. Fischer, on the other hand, reports that, according to the researches of Professor Loeb (Chemical Institute of the Rudolph Virchow Hospital), in three cases the presence of arsenic was discovered in the urine, although in some of them only in small quantities—in the first case, eleven and thirteen weeks after the subcutaneous dose of 0·15 gramme; in the second, eight and ten weeks after ; and in the third case, seven to eight weeks after the injection. Fischer concludes from this that arsenic may still be circulating in the body almost three months after the injection.

Nearly all teachers agree that an injection of arsenobenzol has a very good effect on the patient's general condition, which is frequently evidenced first of all by considerable increase in weight. Ac-

cording to Wechselmann, many patients feel "as if they wanted to drag up trees." He and other authors have even been able to testify to increased potency. As I have already stated above, it has been possible to observe these specific arsenic effects with atoxyl and atoxylate of mercury. True, other authors have also reported marked emaciation.

6. Effect of Arsenobenzol on Syphilitic Diseases of the Primary, Secondary, and Tertiary Periods.

The first reports of the effect of arsenobenzol on syphilitic diseased tissues were made by Professor Conrad Alt, of Uchtspringe, on the occasion of a lecture delivered before the Magdeburg Medical Society in March, 1910. From January 31, 1910, up to the time of publication, in common with Dr. Schreiber at the Magdeburg Old Town Hospital, Alt had treated twenty-seven cases of florid syphilis by

means of a single injection of 0·3 gramme of the new preparation, "and has had quite startling results to report." Alt briefly summarises the facts as follows: "The initial sores showed marked diminution at the end of a few days; the indurating action was also reduced; the maculo-papulous eruptions, which were partly of a moist and ulcerating character, had become paler in colour or had dried up, and then healed, leaving behind flat pigment flakes. Ulcerations on the labia healed quite smoothly within a few days. Large, swollen papules on the anus and vagina lost colour and flattened very soon, and in a few specially severe cases disappeared without leaving a trace behind after four weeks' treatment. Further, a very large, obstinate tertiary ulcer on the thigh is now almost completely cicatrised after hardly three weeks' treatment. The numerous cases of specific angina with difficult coatings, which are generally very obstinate, were reduced most rapidly."

According to the first reports of Wechselmann, even with the most sceptical criticism there could no longer be any doubt as to the rapid and fundamental action of the new drug on the symptoms of syphilis in all their infectious forms, in a way that had been impossible with any previously known remedy. "The curative effects are so rapid that the patients cannot be exhibited, because generally after a few days there is nothing more to demonstrate, and they leave the hospital."

Unfortunately, the great expectations were only partly fulfilled, which were anticipated for this drug, as the result of the first enthusiastic and favourable reports of Alt, Wechselmann, and others. The longer the observation period of the cases treated lasted, and the more teachers received arsenobenzol for the treatment of syphilis, the more was it recognised that this new arsenic preparation of Ehrlich's, although it is true it developed a very good therapeutic action on manifest syphili-

tic symptoms in most cases, did not effect a complete cure of syphilis in the sense Ehrlich anticipated, and certainly this cannot be obtained.

If we group together the opinions of the teachers who have been able to work with this preparation, and the results of their experience with it, reported up to the present,[1] regarding the therapeutic effect of arsenobenzol on the forms of disease of the various syphilitic periods, the result is as follows :

(*a*) PRIMARY AFFECTIONS.

As we have already seen, Alt states that the primary sores were markedly reduced within a short time, the indurations disappearing after a few days. With one patient, who was injected by Wechselmann on July 18, 1910, for about twenty roseola specks on the trunk, and a greasy crusted erosive chancre on the penis, the chancre was already clean by the follow-

[1] Up to the beginning of December, 1910.

ing day, almost without induration, and on June 22, it was closed down to a residue the size of a lentil. With the same patient, a destructive deep-seated primary affection, the size of a five-shilling piece, situated in the lower lip, together with a maxillary bubo the size of a goose's egg, had been anointed in May, at first without any great effect. On May 20, 0·4 gramme of "Ehrlich-Hata" was injected intramuscularly. On June 2, the ulcer was flat, the size of a penny, and the gland was quite small and almost healed on June 8. In cartilaginous primary forms, in the experience of Wechselmann, Miekley, and others, the cleansing process proceeds very rapidly, but the complete cure lasts longer, corresponding to the absorption of the tissue proliferation. According to Dörr, Ivensen, Juliusberg, Schreiber, and Zeissl, the phenomena of the primary affection are rapidly reduced, generally more quickly than with Hg. Neisser has seen the rapid disappearance of the primary symptoms in

many cases, and, further, the curative results of Chrzelitzer, Miekley, Bethmann, and others were surprising in this direction. Spatz stated that ulcerous primary forms were skinned over and softened within six days. Géronne and Huggenberg reported that ten *ulcera dura,* the size of sixpences, had closed up within ten to fourteen days. According to Solomon, also, the average cure of the primary affection, when treated with "606," was effected in a similar period. Herxheimer considers that the primary affection requires on an average eight to fourteen days to disappear. In four cases, however, the indurations remained almost unchanged during the first three weeks. Grouven and Fränkel saw the primary affection frequently recede within a few days. Pinkus considered that, on an average, nine days was required for this. Iversen, however, reported that primary sclerosis and glandular swellings persisted the longest in consequence of the anatomical conditions, but then became softer, and

gradually melted away. Their complete disappearance would certainly be effected within three to four weeks. Spiethoff saw primary syphilis completely epithelialised within one to three weeks. Phimoses, which had appeared as the result of primary affection, receded altogether without any local treatment in about three weeks with a dose of 0·3 gramme, and after six days with one of 0·6 gramme. L. Michaelis similarly considers that an injection of "606" is quite sufficient to cure primary syphilis, without any local treatment, within one to three weeks. Jadassohn also saw a very rapid and prompt result obtained on the primary affection with arsenobenzol. In Welander's experience, the primary affection skins over very rapidly, but induration persists for a long time. Géronne later came to a similar conclusion. Gennerich also was able to testify to severe sclerosis in several cases even after three or four weeks, whereas superficial primary forms only slightly indurated were often

skinned over and softened two to three days after the injection. Rille found that the shortest time required for healing the primary affection was seven days, the longest twenty-four. Pick frequently observed rapid epithelialisation of exulcerated scleroses. Schulz reported that primary forms healed on an average within five to eight days after the injection. Halberstädter also considers that here there is generally a prompt and rapid retrogression. According to Duhot, the chancre disappears within three to thirteen days, having regard to whether it is indurated or not. The experience of Halberstädter, Deneke, and Schindler, with scleroses of the lips, was that these were influenced relatively slowly, or not at all, by the new preparation.

Less favourable results of the effect of arsenobenzol on primary syphilis, despite higher doses (0·5 to 0·7 gramme), were recorded by Stern, who was obliged to have recourse to local treatment with calomel.

Sclerosis of the portio appears to be most obstinate in resisting the curative effect. In nine such cases, the average duration of the healing process, according to Glück, was eighteen days. The observation of Sieskind is interesting, that after the disappearance of the scleroses in the treatment of *chancres mixtes*, ulcers of the character of *ulcus molle* still remain behind, which are uninfluenced by arsenobenzol.

Now, how does the case stand with regionary syphilitic lymphatic glandular swellings, which are known to appear a short time after the primary affection, and even before the outbreak of the general phenomena? From my experience, and that of most other authors (Blumenfeld, Schulz, von Zeissl), these are in part very favourably influenced therapeutically by the new preparation. Blumenfeld records a case of strumous bubo, which diminished within eight days to about a fifth of its original size. True, it is but seldom that it disappears altogether.

Pinkus states that a diminution of the regionary lymphatic glands can regularly be observed, but without these disappearing completely. In most cases lymphatic cords and smaller lymphatic glandular swellings are left behind (Géronne and Huggenberg). In Miekley's experience, on the other hand, these glands only recede very gradually; apparently they are the slowest to be influenced of all the diseased tissues.

(*b*) EARLY STAGE OF SECONDARY SYPHILIS.

It appears from the results and opinions of most teachers, that the most favourable influence of arsenobenzol is obtained upon the phenomena of the secondary stage of syphilitic diseased tissues of the mucous membranes. Spiethoff saw mucous plaques completely disappear two to three days after the injection. According to the statements of Géronne and Huggenberg, in specific angina the plaques healed within seven to ten days. Isaac also observed

similarly rapid healing of plaques and condylomata of the mucous membrane. Severe erosive and papulous diseases of the mucous membrane reacted specially sympathetically, while a previous mercurial treatment had remained without result (Grouven and Fränkel). It appears from Miekley's communications that the coatings on the tonsils melt away during the first days following the injection, so that this may be compared to the effect of Behring's serum on diphtheritic surfaces. The splitting and moderate hyperplasia of the tonsils remaining soon disappear. Frequently on the eighth day after injection the angina is perfectly cured. According to the observations of Glück, it is only the redness of the pharyngeal organs which persists so long, while the plaques on the tongue, tonsils, and soft palate have disappeared at latest five days after the injection. In specific hoarseness the voice has cleared three to eight days after the injection (Blumenfeld, Glück, and others).

The effect of the injection of arsenobenzol was equally rapid in simple maculated exanthemata (Wechselmann, L. Michaelis, Kromayer, Spiethoff, Spatz, Gennerich, Dennecke, Rille) ; they generally disappeared within the course of a few days (Brändle and Clingestein, and others). Miekley alone testified to the surprisingly slow softening of the roseola, pigment of which was often visible several weeks after the injection, with simultaneously persisting hyperplasia. Sieskind confirmed this statement in the case of *roseola urticata*.

Papulous and pustulous syphilides disappeared rapidly and dried up (Spiethoff, Dörr, Iversen, Miekley). In papulous exanthema as a rule a slight pigmentation is left behind (Chrzelitzer and others). A papulous crustaceous exanthema had dried up completely at the end of two days after 0·6 gramme, and the crusts had fallen off (Spiethoff). According to Sieskind, it is only the micropapulous and

lichenoid exanthemata respectively which respond to a certain extent favourably to arsenobenzol; whereas one can assert of the large papulous syphilides that they appear to be refractory to "606." Ulcerous syphilides also, and even *rupiæ syphiliticæ*, can be rapidly cured (Isaac, Brandenburg, Juliusberg). Moist papules dry up and flatten out, often in a short time (Spatz, Géronne and Huggenberg, Miekley), but still they may persist for a fairly long time (Welander, Schreiber, Ledermann). Condylomata form new skin visibly, and often disappear with almost miraculous rapidity (Grouven and Fränkel). An excellent therapeutic effect has been obtained with arsenobenzol, according to Volk and Lipschütz, in renitent syphilitic paronychia. *Psoriasis palmaris* and *plantaris* had disappeared at the end of ten days (Géronne and Huggenberg, Saalfeld), but Bruhns stated that several cases of specific psoriasis had been very obstinate. Wechselmann once saw a *leucoderma colli*

disappear within a few days, while the white places healed up. In contradistinction to this, there are the observations of Volk and Lipschütz, among others, that leucoderma especially remained uninfluenced by " Ehrlich-Hata."

Generalised lymphadenitis, as well as isolated glands in the secondary stage, may disappear within the course of a few days (Dörr, Spiethoff, Sieskind), or at least show a marked inclination to recede (Hoffmann, Grouven, and Fränkel). On the other hand, in the experience gained at the Lesser Clinique, it is especially the glands in the secondary stage which are longest in reacting to the influence, as already mentioned.

A hæmorrhagic exanthema of the leg receded at the end of eighteen days ; a severe impetiginous syphilide under the hair of the head, and one on the back, disappeared after sixteen and twenty-one days respectively (Géronne and Huggenberg).

Headache, the appearance of which is

specially characteristic of secondary syphilis, often disappears at the end of twenty-four hours (Blumenfeld, Neisser, Halberstädter, Sieskind). Syphilitic bone disease reacts promptly, according to the experience of Sieskind and others.

The most difficult to influence are apparently anal papules (Brändle and Clingestein) and hypertrophic papules (Volk and Lipschütz), as well as more severe papulous exanthemata (Hoffmann), especially the hard cutaneous papules, which, in Wechselmann's experience, only disappear at the end of two to three weeks.

Most authors, as is evident from the foregoing references, are able to testify to very good results, as regards the momentary curative effect, especially with the diseased tissue of early secondary syphilis. In the experience of other teachers, however, the clinical phenomena of this period did not disappear with such striking rapidity (Bruhns). In some instances the effects were slow and unsatisfactory (Kromayer),

and often not more rapid than with Hg treatment (Saalfeld, Ledermann, Buschke, Volk, Blaschko, and Lipschütz).

In the treatment of certain cases in the early secondary period, the phenomenon of the Jarisch-Herxheimer reaction was mostly observed (by Truffi, Wechselmann, Neisser, Herxheimer [in 60 per cent.], Chrzelitzer, Kromayer, Halberstädter, Wolters, Volk and Lipschütz, Hoffmann, myself, and others). This phenomenon is known from mercurial therapy, and expresses itself chiefly in the fact that often twenty-four to forty-eight hours after mercurial treatment has been inaugurated there is an increase of the existing exanthemata. Before the discovery of the *S. pallida,* this circumstance was frequently brought forward for diagnostic purposes, in order to determine whether isolated flakes present, which were only just visible, might be pronounced as roseola or not. Ehrlich regards the Herxheimer reaction in the "606" treatment and

similar phenomena as an inadequate action of the injection. In his opinion, in such cases the parasites are not at once destroyed, but, instead, only irritated, and in this condition produce an increased quantity of toxines. If the Herxheimer reaction appears in exanthemata, Sieskind believes that it must be regarded prognostically as an unfavourable sign.

Besides this "local" reaction, A. Neisser distinguishes a "general" one in the treatment with arsenobenzol, which is characterised by transitory increase of the headache in cerebral syphilis, and of the irritant spinal phenomena in tabes.

In treating syphilitic infected tissues of the primary and secondary periods, it is naturally of great interest and importance, in estimating the effect of arsenobenzol, to study the behaviour of the spirochætes after one injection. In many of these forms of disease they can be distinguished more or less easily, and generally in greater numbers. (In the tertiary and malignant

forms it is known that this does not succeed, or only very rarely.)

By means of animal experiments (Hata, Tomasczewski, Uhlenhuth, and the author) we know, as already mentioned above, that the spirochætes have disappeared from the infected tissue of experimental syphilis and of spirillosis of fowls sixteen, twenty-four, or thirty-six hours after the injection of the dose of arsenobenzol. In man, according to Sieskind, Schreiber, Sellei, and Glück, they mostly disappear at the end of a day from the manifested phenomena of primary and secondary syphilis. If spirochætes can still be detected on the second day after the injection, these appear swollen and altered in their motility.

According to Spiethoff's observations, the spirochætes disappear from the irritant serum, on an average, twenty-four to forty-eight hours after the injection. In thirty-two carefully controlled cases, Scholtz saw the spirochætes disappear permanently at

the end of twenty-four hours fifteen times; twelve times they could be detected for two to three days; and only five times were they evident longer than four days. Iversen punctured the glands in ten cases of very pronounced primary lymphadenitis a few days before treatment with "606" as well as a few days after. In all these cases, he was unable to discover any spirochætes in the glandular juices three to five days after the injection, whereas before they had been present in great numbers.

True, Hoffmann proved that in a series of cases spirochætes were not evident on the surface of papules and plaques after twenty-four to seventy-two hours. He had, however, seen cases where they were still to be found in perfect motility on the genital and tonsillar papules at the end of eight days.

In one case of papules of the mouth and anus, which had reappeared twelve days later, despite a successful Ehrlich-Hata in-

jection, Oppenheim found numerous well-preserved *Pallidæ*. According to Bruhns, in many cases the spirochætes had already disappeared at the end of two days, whereas in others they were still present later. Grouven was able to prove the presence of living well-preserved spirochætes in a facial papule at the end of two months.

Fürth, in sclerosis of the urethral orifice, saw lively mobile spirochætes seven days after an arsenobenzol injection, and after the chancre had healed.

If at the end of twenty-four to forty-eight hours the spirochætes have not yet disappeared, this, in the opinion of Ehrlich, is an indication that either the dose was too small, that the absorption was inadequate, or that one had to do with an arsenic-fast strain of spirochætes.

Hecker only attributes slight importance to the negative spirochæte result in specific efflorescences a few days after the injection of Ehrlich-Hata "606." Although in some

of the cases he treated the spirochætes disappeared promptly, a little later relapses, with numerous spirochætes, set in at these places.

Moreover, in two cases of congenital syphilis in which the patients died two and four days after the injection of arsenobenzol respectively, Herxheimer found no specific spirochætes in any of the organs, with the exception of the lungs. Here, the spirochætes appeared to be agglutinated and degenerated to the fullest extent up to complete disintegration. Herxheimer considers that the enormous syphilitic spirochæticide action of the new drug is especially demonstrated in these two cases, in that a large quantity of spirochætes are almost constantly found in the internal organs in cases of congenital syphilis.

Gerber was able to testify to the distinctly destructive influence of arsenobenzol on the spirochætes of the mouth in one case of severe tertiary syphilis. Reference must also be made to the spirillicide

effect of this preparation in the curative results obtained with "606" in Plaut-Vincent's angina (Rumpel).

(*c*) THE LATE STAGE OF SECONDARY SYPHILIS AND TERTIARY SYPHILIS.

It is just in these periods that the most obstinate forms of the disease often occur, which are either uninfluenced by specific mercurial or iodine therapy, even when administered in the strongest doses, or are only affected very slightly and slowly. In the manifold and frequently severe disturbances of tertiary syphilis, the therapeutic action of the new Ehrlich preparation is generally found to be most effective. Wechselmann gives the following report of the excellent effect of arsenobenzol in one case :

A patient had developed the primary symptoms seven months previously, and an eruption appeared four weeks later. From November 28, 1909, to the middle

of March, 1910, he was given thirty-five injections of hydrarg. sal and calomel. For three months he had had pain in the joints of both knees. On May 5, 1910, he came under Wechselmann's treatment. "The patient is emaciated to a skeleton; his skin is as pale as a corpse, and his face like a death's-head, with an intensely painful expression." On the face and body there were ulcers and cicatrices the size of sixpence (ten pfennige), and even bigger, covered with crusts, and extending down to the subcutaneous cellular tissue. An odious smell proceeded from the nose, in which the septum was perforated, and the left lower muscle and vomer were about to be shed. He had intense pain in swallowing, and had to be fed with pharyngeal probes and nutrient enema. The pulse was very small, with bad tension, and was 120 and more. As his condition constantly deteriorated under iodine injections, and a fatal issue was anticipated within a conceivable time, he was injected

by Wechselmann on May 21, with 0·4 gramme "Ehrlich-Hata." This was not followed by any rise of temperature, and the pain remained moderate. Even at the end of two to three days the patient's general condition had improved distinctly, and on May 26, general recovery began. The diseased bony nasal framework fell off altogether, and the fœtor disappeared. On May 30, the ulcers were responding perfectly to the healing process, or were completely healed. The patient had increased in weight from 41·5 kilos on May 21, to 49 kilos on June 22 (according to Bressler).

An equally brilliant result is recorded by Michealis in one case: A patient became infected in 1906, and, despite treatment in 1907 with mercury, atoxyl, and iodide of potassium, ulcers appeared in the gums on the right and left of the uvula, and, further, a saddle-nose had developed. The uvula was only hanging by a stalk, "and it might drop off any day." Three days afterwards the surroundings of the walls

of the ulcers were red, and eight days after the injection only small fragments of the former ulcers remained on both sides of the uvula. In two cases of very extensive ulceration of the thigh and subcutaneous gummata with exposed bones, Kromayer observed an extraordinarily rapid absorption of the infiltration and quick skinning over of the ulcers. "The epithelisation occurred in a formerly unknown manner." According to Iversen, an excellent curative effect is shown especially in ulcerous processes, gummata, and gummatous wounds. Glück reports that in three cases of gummata of the larynx an injection of arsenobenzol practically saved the patients' lives. Spiethoff records one case of tertiary nasal syphilis in which, twenty-four hours after an injection of 0·6 gramme of "606," the purulent secretion of a disintegrated gumma located in a muscle ceased. The ulcer had closed by the second day, and only slight infiltration remained. A patient who had been antisyphilitically treated in

several ways from 1906, and was now suffering from an unusually large gummatous ulcer, was injected by Ledermann with 0·5 gramme of Ehrlich's preparation. The necrotic eschar of the ulcer fell off the day after the injection; two days later the skinning over began; and on the thirteenth day half of the ulcer, which was the size of a hand, was closed. The epithelial margin pushed forward daily from ½ to 1 c.c.

Herxheimer treated nine cases of retarded (secondary) syphilitic phenomena (tuberous syphilides and gummata). Periostitis of the vault of the cranium disappeared after seven days (there was intense swelling on the fourth day); a gumma of the left tonsil disappeared in six days after 0·3 gramme; multiple gummata of the hard and soft palates in ten days after 0·45 gramme. An ulcerated gumma of the left testicle, the size of the fist, receded rapidly at the end of twenty-four hours, after 0·5 gramme (the patient had tubercle

of both lungs). A gummatous disintegrated hard and soft palate, which had been refractory to mercurial and iodine treatment for seven years, healed so rapidly that at the end of a week the patient could again eat solid food, and at the end of three weeks there were only quite small fragments remaining.

In one case of testicular and cerebral syphilis, Wechselmann was able to effect a cure in about four days after an injection of 0·405 gramme of "606." Géronne and Huggenberg saw an orchitis gummosa, the size of a small fist, shrink almost to the size of the healthy testicle within sixteen days after the injection. Isaac stated that a serpigino-ulcerous syphilide, which had appeared four years after the infection, together with disintegrated gummata on the roof of the larynx and papules on the vulva and anus, healed completely within ten days of the injection.

Meirowsky, amongst other things, records the prompt cure of large tertiary

ulcers of the hard palate and of the vault of the cranium after the injection of arsenobenzol. Wolters describes the influence of the Ehrlich preparation on advanced forms of syphilis as generally startling. "Ulcerated gummata heal in a surprisingly short time. Bony processes, after a very energetic reaction (pain), at first show a slow but constant recovery." Aschaffenburg and Gesser were able to testify to a brilliant result in a case of cerebral syphilis. According to the reports of von Zeissl, gummata of the mucous membrane of the mouth, tongue, and throat clear up, so that patients can soon take solid and liquid food without hesitation. Cutaneous malignant syphilis (one large and one small gummamatous syphilide) healed rapidly under "606," whereas the previous injections with insoluble Hg had remained unsuccessful. Periostitis of the end of the radius, which was of some years' standing, diminished visibly within four days, and the pain disappeared altogether.

Ehrlich himself records one case which shows very markedly the rapid action of arsenobenzol in diseases of the pharyngeal organs: "A patient with gumma of the tonsil, who for two months had been treated without result, was given an injection at two o'clock; five hours later the medical man was able to testify to the fact that the patient, to his great joy, had been able to swallow a piece of bread-and-butter without pain."

Chrzelitzer saw a laryngeal gumma disappear at the end of four days. Friedländer reported the extraordinarily successful result of this treatment in fifteen cases of severe ulcerations and gummatous processes in the mouth, nose, larynx, and trachea.

Weber was able to report a very good result in a case of severe cerebral syphilis and specific meningitis. Within a few days recovery took place, and the markedly disturbed pupillary reflex, speech, and power of movement of the right side

returned, as well as complete mental power. Gennerich found, from experience, that cerebral syphilis offered a specially favourable domain for Ehrlich-Hata treatment. "In many cases here it is life-saving; in others it preserves whatever there is to preserve." In one case of cerebral syphilis (*arteritis obliterans*) I observed and treated, it was not possible to save the patient with an injection of 0·5 gramme arsenobenzol. It is true the case was very far advanced in the secondary period, with flabby paralysis of the left side, as well as facial paralysis. Miekley has also seen extraordinarily favourable results in the treatment of tertiary syphilis. Thus, a muscular gumma on the ulnar side of the left forearm, which was the size of a large goose's egg, diminished to that of a pigeon's egg four to five days after the injection, and healed completely in under fourteen days. Tertiary ulcers of the leg only required a week and a half for complete cure. A deep ulcerous thrombophlebitis of the knee diminished within

fourteen days to the size of a sixpence (ten pfennige). Miekley, as the result of these observations, summarises his opinion of the effect of arsenobenzol on tertiary syphilis as follows : " The graver the case, the more surprising the effect."

In the experience of Zieler, Bayet, and others, on the other hand, it is not always possible to prove the superiority of arsenobenzol over mercury in tertiary syphilis. Thus, Zieler states that out of thirteen such cases, only four were favourably influenced.

(*d*) MALIGNANT SYPHILIS AND ULCEROUS TERTIARY FORMS RESPECTIVELY.

The same thing appears to apply to malignant syphilis and early ulcerous syphilis respectively, as has been said of the curative effect of arsenobenzol in tertiary forms.

According to the researches of Grouven, Hoffmann, Ledermann, Juliusberg, and

most other authors, malignant syphilis is influenced equally favourably. In two cases of malignant syphilis, in one of which a fatal prognosis had been given, Dörr also saw excellent results, both with regard to the cure of the infected processes as well as in marked improvement of the general condition. Pick observed the disappearance of the symptoms (of pharyneal ulcer and gumma, and papules of the tonsil, respectively) a few days after the injection, in two cases of malignant syphilis, in which iodine and mercury had been ineffectual. Grouven and Fränkel perceived the influence of arsenobenzol treatment especially distinctly in a case of extensive ulcerous formations on the leg, which skinned over and cicatrised in the very shortest time. Brändle and Clingestein obtained most excellent results, especially in the treatment of malignant syphilis. As Herxheimer has mentioned, three cases of malignant syphilis responded very well. In one of these cases, large ulcers of the

entire skin of the head, of the hard palate, the throat, and tongue, healed in ten days with 0·4 gramme, without local treatment. From the report of 375 cases treated with the Ehrlich-Hata preparation, collected by Sieskind, it appears that symptoms of malignant syphilis and lues præcox offer the most gratifying field for treatment with "606," therefore just those cases which are commonly known as the gravest in syphilis. Meirowsky, on the other hand, was unable to distinguish the slightest therapeutic effect after the intravenous injection of 0·4 gramme arsenobenzol in one case of malignant syphilis. Relapses were observed in three cases of malignant syphilis by Gennerich. One directly unfavourable effect of the Ehrlich-Hata treatment was seen by Fischer in a case of this description, which was also refractory to all Hg and iodine therapy.

For the rest, it is remarkable that apparently the best, and perhaps also the most lasting, effect of arsenobenzol is

testified to in the tertiary and malignant forms of syphilis respectively, although in these products one can never, or at most only very rarely, verify the presence of isolated spirochætes. In my opinion, the principal part is played here by the *rebounding* factor of the arsenic preparation, which excites the tissue to fresh activity.

(*e*) TREATMENT OF SYPHILITIC DISEASES OF THE EYES WITH ARSENOBENZOL.

I should like to class together in a particular group the cases of specific diseases of the eyes which have been treated with Ehrlich-Hata "606." After the experience with atoxyl and other arsenic preparations, it was precisely here that one feared there might be an occasional unfavourable effect of the arsenobenzol. Sieskind saw four cases of iritis papulosa promptly improved. Glück treated two cases of specific ophthalmic disease (keratitis parenchymatosa and iritis) with very good success.

Von Zeissl saw a case of iritis disappear four days after the injection; a paresis of the accommodation was very favourably influenced. I myself saw a bilateral specific iritis with posterior synechia disappear promptly and rapidly. Fehr and Seeligsohn obtained good results in episcleritis and iritis.

Grôsz treated eight patients with fresh specific disease of the eyes, amongst them a case of *ulcus durum conjunctivæ*, with arsenobenzol, and was able to prove that this drug is very effective in specific ophthalmic disease.

Good results have also been obtained in hereditary syphilitic eye affections with Ehrlich-Hata "606" by Grósz, Treupel and others, without injury to the optic nerves. Schanz has successfully treated five cases of keratitis parenchymatosa. In some cases in which the visual nerves were not quite intact (fresh neuritis optica) Wechselmann has even employed arsenobenzol successfully without arousing any kind of dis-

turbances in the disease itself. In six cases also of commencing or advanced atrophy of the optic nerves, he has given the injections without increasing this. Anscherlick has also twice made an injection of "606" in diseases of the eyes without being able to perceive that the optic nerves had been injured in any way. Exudative processes of the choroid and of the retina respectively were favourably influenced. In one case of atrophy of the optic nerves, Glück was unable to obtain any therapeutic result. Neither could Igersheimer discover any influence on the corneal process in a case of congenital specific corneal disease, after an injection of 0·4 gramme of "606," although the Wassermann reaction was negative. Wechselmann calls attention to the fact that in over 1,400 cases, which he has treated with arsenobenzol, he has never observed amaurosis or any other kind of disturbance of the visual apparatus, and that even with the great number of injections which have been made by now—in his

estimation, 20,000—nothing of the kind is known.[1]

Despite all these good results in specific eye diseases, it is, in my opinion, absolutely necessary first of all to convince oneself that the visual nerves are perfectly healthy before an injection of arsenobenzol is given. Wechselmann has recently expressly demanded that there should be a thorough ophthalmological examination of the eyes, occasionally from the specialist's side, particularly of the field of vision. Cases in which the optic nerve is not quite intact would be better excluded from treatment with arsenobenzol, for reasons which I shall mention when discussing the secondary effects of atoxyl, especially if there is a question of repeating the injections. One must wait to see whether this will not cause injuries of the optic nerve, like atoxyl; as far as my knowledge goes, it is only after protracted atoxylic treatment that amauroses have been observed,

[1] See Secondary Effects, p. 172.

and not after only a single larger dose. Syphilitic diseases of the eyes without participation of the optic nerves can naturally be subjected without hesitation to treatment with arsenobenzol, as is evident from what has been stated in the foregoing pages.

(*f*) SYPHILIS OF THE INTERNAL ORGANS.

Very good curative effects are often obtained in specific diseases of the internal organs, which fall into this period. Thus, F. Lesser has recorded the case of a patient with severe pulmonary syphilis, who was treated and cured with the Ehrlich preparation. Simultaneously, L. Michaelis stated that he had been able to observe distinct improvement, both in chronic amyloid as well as in acute syphilitic forms of nephritis, when treated with arsenobenzol. In two cases of syphilis with nephritis, Scholtz saw recovery in one case and distinct improvement in the other.

According to the observations of Alt, Weber, and others, as I have already mentioned, cerebral syphilis forms a very gratifying and convincing object for treatment with arsenobenzol.

Meirowsky reports a favourable influence on syphilitic nephritis, which, however, was not permanent. As Wolters recorded, a case of incipient diabetes on a specific basis was also favourably influenced. According to Duhot, gummatous internal diseases are cured with the same rapidity as tertiary ulcers. Géronne successfully treated a case of specific disease of the liver. Gennerich observed that visceral syphilis of six months' duration was free from pain the day following the Ehrlich-Hata injection, whereupon the miserable condition improved. Wechselmann records a case of the healing up of severe ulcerous syphilis of the rectum; icterus of long standing disappeared within ten days. In one case of bilateral labyrinth deafness, according to Grouven and Fränkel, an unmis-

takably distinct improvement in hearing set in at the end of twelve days after a single injection of 0·6 gramme.

(*g*) META- AND PARA-SYPHILITIC DISEASES, INCLUDING TABES AND PARALYSIS.

As is known, the first communications, with regard to the therapeutic efficacy of the new Ehrlich preparation "606" in nervous and mental diseases on a syphilitic basis, originated with Alt. The curative results reported, especially in tabes and paralysis, were altogether so good, and were stated so convincingly, that they aroused the greatest general interest. It seemed as if, in arsenophenylglycin, and more still in arsenobenzol, an effective drug had been found "which might pave the way for the remission of paralysis, and provide a prophylaxis for this terrible disease." Thus, for example, a justice of the peace, who had been admitted to hospital on account of progressive paralysis,

according to the report of Alt at the Berlin Medical Society (Meeting of March 3, 1910), had been completely cured by a single injection of a relatively small dose of arsenobenzol and was again able to transact his business thoroughly well. To-day, unfortunately, we know that it is just these syphilitic nervous diseases, and especially the most terrible forms of them, tabes and paralysis, which are least influenced by Ehrlich-Hata "606," and generally not at all. Proportionately, even Alt had soon to restrict his earlier opinion as to the efficacy of arsenobenzol. He stated that a favourable action of this drug was only to be expected at the beginning of tabes and of paralysis—to a certain extent, when the "first lightning pains" set in.

In the early stages of so-called "tabo-paralysis" it appeared to Alt that treatment with the new Ehrlich preparation was specially indicated, and was very efficacious. In the case of those suffering from spinal

paralysis, Alt's experience was that in the early stage their chief trouble was removed by such treatment; this was demonstrated chiefly by continuous marked diminution of their previous unbearable pain. Thus, the shooting pains especially were said to cease at one stroke. Wechselmann also was able to testify to a distinct improvement in the sense of constriction, of headache, of intercostal neuralgia, and of weakness in the muscles of swallowing and of the bladder, in patients suffering from tabes.

Selley was able to confirm the statements of Alt to this extent—that he had been able to obtain a two-months' cessation of gastric attacks, from which a patient with tabes suffered, by treating him with arsenobenzol. True, the attacks returned at the end of that period. He saw an improvement of dysarthria in paralysis.

Torday does not expect much in advanced cases of tabes and paralysis. "If, however, there are manifest syphilitic

symptoms present, one can naturally administer arsenobenzol as an anti-syphilitic procedure."

Favourable results were obtained in paralysis to a certain extent by Dörr, Treupel, Duhot, Michaelis, and others. In treating nervous patients on a specific basis, Friedländer has also observed a favourable effect on existing pain.

Glück was twice unsuccessful in advanced paralysis, and so was Géronne in twenty cases of different syphilitic sequelæ. Behring saw no effect in six cases, and Meyer none in sixteen. Further, von Zeissl was unable to testify to any specially favourable results in similar diseases. Ledermann had to report failure in a case of facial paralysis on a specific basis, and with a patient with paraplegia of both legs. Salmon, on the other hand, in two cases of hemiplegia without contracture, was able to testify to cure in one case, and at least to distinct improvement in the other. In his opinion, the drug is contra-

indicated in progressive paralysis. Schreiber saw marked improvement in a large number of epileptic cases, which were due to syphilis.

I will not here go farther into the records, which for the most part can only be regarded as problematical, up to the present. We must wait until reports have come in of extensive employment in large psychiatrical institutions and longer periods of observation have elapsed. I should like, however, to join issue with Grouven in the opinion that, at the present time, the first "lightning pains" of para-syphilitic diseases should not form the absolute limit of our therapeutic treatment with arsenobenzol, and that in all cases of tabes and paralysis, where fresh symptoms are still present, they should be subjected to treatment with this drug (A. Neisser). True, the greatest caution is required in all diseases of the central nervous system, and, according to von Zeissl, those cases should be excluded in which destruction

has already set in. As with such patients, disturbances of the blood-pressure and of the circulatory apparatus may arise (Alt, Schlesinger, and others), Schlesinger recommends that it might be well to administer a cardiac a few days after or before the injection. "Strict asepsis is important, five days' unconditional rest in bed, corresponding diet, and regulation of the bowels. It is advisable that magnesia usta should be administered internally" (von Zeissl).

(*h*) HEREDITARY SYPHILIS.

As far as I am aware, the first case of congenital syphilis was treated with arseno-benzol by Wechselmann, who effected a cure with it in a short time in an infant with a severe partly pemphigoidal syphilide. Two other infants with pemphigus neonatorum were also cured. Michaelis showed a child before the Berlin Medical Society, in whom, after an injection of

0·06 gramme of the new Ehrlich preparation, the symptoms of hereditary syphilis—maculo-papulous exanthema, with infiltrations on the soles of the hands and feet—had disappeared within eight days. Only choryza remained behind. Recovery had commenced on the second day. Pick obtained a rapid curative effect in a case of hereditary infantile syphilis—lues cutanea maculosa, papulæ frontis, palmæ et plantæ. In the Lesser Clinique five infants with hereditary specific disease, with the most varied symptoms (pemphigus neonatorum, Parrot's pseudo-paralysis of the arm, large papulous syphilide, rhagades around the mouth, choryza, etc.), recovered completely very rapidly after intragluteal injections of 0·03 to 0·05 gramme of "606." According to Spiethoff, Fränkel and Grouven, Pick, Junkermann and Kalb, surprising results are often obtained here with arsenobenzol treatment. Hoffmann treated with 0·3 gramme a fifteen-year-old congenital syphilitic youth, with ozæna syphilitica, excessive caries,

intense headache, paralysis of the left abducens, and protuberance of the bulb. The symptoms of the disease were surprisingly improved; the bulbar protuberance and the abducens paralysis disappeared altogether.

The *Medizinische Klinik*, on the other hand, reports that, from the private communications of different teachers, the Ehrlich-Hata drug apparently fails in a relatively small number of cases of hereditary syphilis.

Moreover, Wechselmann recommended that only well-nourished children should be subjected to the new treatment with arsenobenzol. "Through the rapid liberation of colossal quantities of spirochætes, on the administration of '606,' such a number of endotoxines were released, that a temporary injury was caused, which the child's organism could not stand."

Particular interest was aroused by a communication from Taege, on the good therapeutic result obtained in the case of a

syphilitic infant, by treating its nursing mother with arsenobenzol. A young woman, with manifest syphilitic symptoms, had given birth to a colourless, shrivelled, old-looking, apathetic child, weighing 2,400 grammes, on July 4, 1910. On July 13, the child developed pemphigous blisters on the soles of the feet and paronychia on the hands. On July 14, the mother was given 0·3 gramme of arsenobenzol; from the third day onward a surprising diminution of the condyloma and disappearance of the spirochætes was perceptible. On the same day the syphilitic symptoms of the child, which up to now had increased in intensity, simultaneously came to a standstill, and then suddenly all of them began to recede. On the fifth day the skin looked pink, the paronychia had disappeared, and likewise the pemphigus up to a small patch. On July 29, the child weighed 3,900 grammes, and exhibited no further specific symptoms. Taege assumes that antitoxines had been transferred into

the child's organism through the milk, which had been formed from the endotoxines liberated in the mother's organism from the disintegrated spirochætes. Taege claims, therefore, that for syphilitic children the syphilitic mother should be treated with "606." If she is not able to suckle her child herself, then a syphilitic wet-nurse should be procured, and treated with arsenobenzol before commencing her duty, a demand which at the present time appears somewhat hazardous.

Duhot describes an analogous case. He is, however, of opinion that an insufficient quantity of spirochætes are destroyed in the child's organism by taking the anti-infectious substance through the mother's milk. He, therefore, recommends that the child itself shall also be treated with "606." As Ehrlich mentions, similar cases have been observed by Raubitschek, Dobrowicz, and others. Ehrlich agrees with Taege's conclusions; still he advises that such children should have a small dose of arseno-

benzol injected, in order to destroy any remaining spirochætes.

Meirowsky was able to cure pemphigous blisters in a child with hereditary specific disease, by injecting serum taken from syphilitic patients who had been treated with "606."

Similarly, Marinesco, Plaut, and Scholz observed a favourable influence on syphilitic products, especially those of congenital syphilis, by injecting serum from patients who had been treated with "606." In my opinion, it is not yet clearly decided whether an action of this kind, of mother's milk and serum, on patients treated with arsenobenzol, should be attributed to traces of arsenic, which might be found in the milk or blood.

The following case, described by Kalb, may be given to a certain extent in contradistinction to those already mentioned: A pregnant woman, who was suffering from fresh specific disease, was treated with an inunction cure during pregnancy and with calomel while suckling. Despite this, the

child, although born without syphilitic symptoms, soon developed firm papules on the face and trunk. Finally, severe visceral syphilis set in, and the child died.

Grouven was able to cure the syphilitic products induced experimentally in rabbits, by means of serum from patients treated with "606."

Von Zeissl mentions that many medical men have had goats and asses rubbed with mercury, and have then fed and cured hereditary syphilitic children with the milk taken from these mercurialised animals.

7. Dosage.

With conceivable caution, at first only small doses of the Ehrlich-Hata preparation "606" were administered for the treatment of human syphilis. As Ehrlich has reported, Truffi used only 0·025 to 0·05 gramme in his first experiments. The transition from the doses of 0·3 to 0·4 gramme, which were originally almost generally employed, to

higher ones has been gradual. According to the clinical observations of most authors, one can go up to from 0·6 to 0·8 gramme with adults, and even to 1·0 to 1·2 gramme, especially with Ehrlich's newest preparation "hyperideal '606,'" which is less toxic, without causing any particular secondary effects. It is only in nervous diseases that Alt and Torday claim, and Ehrlich agrees with them, that small doses should be retained (not exceeding 0·4 gramme), as in these cases one must be very cautious because of the weakness of the whole organism to the new arsenic preparation.

Salmon believes that a smaller dose of 0·3, 0·4, or 0·5 gramme will bring about the disappearance of the syphilide just as quickly as a larger one of about 1·0 gramme.

Schreiber considers that in intravenous injection one should not exceed 0·4 to 0·5 gramme. Weintraub and others inject larger doses, up to 0·7 to 0·8 gramme. Iversen follows up the intravenous injection (on an average with a dose of 0·5 gramme)

two or three days later with an intramuscular one, until altogether a total of 0·8 to 1·0 gramme has been injected.

Ehrlich considers that at the present time it is impossible to give any general figures with regard to the height of the dose; in his opinion this depends upon the quality of the disease.

8. Influencing the Result of the Wassermann Reaction by Means of Treatment with Arsenobenzol.

According to the first communications of Wechselmann and Lange, if the observation period were sufficiently long the Wassermann reaction, which before the injection was positive, would be negatived in 100 per cent. of the specific cases treated with an injection of the Ehrlich-Hata preparation. The time at which the negative result set in appeared to be dependent on the preliminary strength of the reaction before the injection. The strength of the reaction itself should fall into a proportionate curve without any

greater irregular variations. Weber, Gennerich, von Zeissl, Pick, and McDonagh also confirmed the fact that in 100 per cent. of the cases the previously positive reaction was changed into a negative one. According to Gennerich, the appearance of the negative reaction was accelerated by a subsequent second injection of "606." Similar results were obtained by Hoppe and Schreiber; they got a negative reaction in 84·6 per cent. of all their cases; in a later report, however, Schreiber gave this as only 50 per cent. Iversen considers that the positive Wassermann reaction disappears twenty to forty days after the injection, and in some cases even on the eighth to tenth day. In none of the cases treated by Iversen, in which the reaction became negative, did the result again become positive. It happened in a few cases that, soon after the injection of arsenobenzol, the intensity of the Wassermann reaction increased, to again slowly diminish later. The same phenomenon

was observed by Grouven and Michaelis. Spiethoff considers that with this treatment the Wassermann reaction becomes negative after four, six, or eight weeks. "In many cases the reaction gradually ceased, and in others variations set in before the permanent negative phase." Fränkel and Grouven were able to testify to a negative result of the Wassermann reaction three weeks after the injection of a large number of tabetic and paralytic patients. In the other cases, a very considerable change of the conditions became evident in the form of a marked weakening of the reaction. With specific patients, on the other hand, although it is true these authors often saw the reaction distinctly influenced, "frequently, despite noticeable clinical improvement, the sero-diagnostic result remained unvaryingly positive."

Alt also found that there was a negative reaction in a distinctly higher percentage of paralytics than there was of syphilitic patients. In Herxheimer's experience, the

reaction still remains positive in many cases, but in three-quarter of those which were observed constantly it was negative at the end of fifty days. Linser obtained a negative reaction in about 60 to 70 per cent. of the cases, while Kromayer and Stern only got one in 50 per cent.

According to Bering, an occasional change of the reaction sets in after four to five weeks; in forty cases the Wassermann reaction did not alter, while in twenty-six it swung back from a positive to a negative result. Géronne likewise was only able to obtain a negative reaction in thirty-seven out of seventy-seven patients. A second injection rendered nine more cases negative. A. Neisser was at first only able to prove a negative reaction in about 10 per cent., and later in 44 per cent., of cases after treatment with arsenobenzol. This occurred only in those patients who came under treatment very early after infection and after the appearance of the primary affection. Glück only saw a subsequent negative reaction in

five out of twenty cases treated. Schlesinger found the Wassermann reaction after two to ten weeks; Miekley, generally positive after more than two months; Scholtz also considered that the reaction was still positive five to six weeks after the injection. Similar results were arrived at by Loeb, Isaac, Hermann, Brändle, and Clingestein, Anscherlik, Pick, Halberstädter, Bruhns, Torday, and others.

In my cases also the Wassermann reaction was only negative once.

With regard to the result of the Wassermann reaction in hereditary syphilitic infants and children, the same conditions seemed to apply to those which exist in the case of children treated with mercury—namely, a very rare negative reaction. As is known, various authors, including Michaelis and I myself, have proved that in the case of hereditary syphilitic children, it is very difficult to change the positive reaction into a negative one by means of mercury.

As is evident from the foregoing summary of the authors' results, apparently the Wassermann reaction remains positive in a fairly large percentage of cases after treatment with arsenobenzol. True, the majority of these results refer to a single treatment, often only with small doses. It is not possible at present to decide definitely whether, with larger doses and occasionally with repeated arsenobenzol injections, or with intravenous application, this reaction would be negative in all cases, and remain so permanently (Gennerich). Ehrlich considers the behaviour of the Wassermann reaction of the greatest importance in estimating "606" treatment. He says that every case in which the reaction persists after treatment must be taken as uncured. A negative reaction, if it remains lastingly negative, may be regarded as indicative of cure. It is, however, possible that it is only a negative phase, if the reaction subsequently again becomes positive. In that case, according to Ehrlich, the

injection only diminished the number of spirochætes in the organism. The remainder were no longer capable of inciting a positive reaction. But if these had again increased, then the result would again become positive. Ehrlich, therefore, regards a renewal of the positive Wasserman reaction as analogous to a relapse without external symptoms, and hence as an indication to repeat the injection. Taking this into consideration, Ehrlich claims that it will be possible to control the treatment within certain periods, by examining the blood with the Wassermann test. Now, however, even with the Ehrlich-Hata treatment, various teachers have observed that, despite the existence of florid specific symptoms, it is possible for the result of the reaction to be negative. Volk and Lipschütz assert that in one of their cases which relapsed, the reaction was continuously negative. Therefore, too much importance must not be laid on a negative result of the Wassermann test. In mer-

curial treatment, I have detected repeated backward and forward fluctuation of the reaction from a positive to a negative result, and *vice versâ* during treatment. In order to obtain a certain and constant result as far as possible, the blood should not be tested during or immediately after finishing the mercurial cure, but one should wait until some little time after treatment. Similarly, the blood should not be examined immediately after the injection, for one might be deceived by the arise of a so-called "negative phase," when forming an opinion as to the influence of the treatment on the result of the reaction.

The phenomenon observed on various sides (Wechselmann, Neisser, Iversen, and others), that in many cases a reaction which was originally negative became positive after the injection, is explained by Ehrlich by the fact that the spirochætes present before treatment were not sufficient to incite a positive reaction. These spirochætes, however, were liberated by the

injection of arsenobenzol, and their endotoxines freed. These became absorbed, and thus brought about a positive result. Citron considers that this phenomenon is simply due to the fact that the examination, and injection respectively, were undertaken shortly before the reaction had become positive. If one had only waited a short time, then the reaction would have become positive without an injection.

9. Relapses.

Wechselmann stated, in March, 1910, that he received the new preparation "606" from Privy Councillor Ehrlich, and had not been able to discover any relapse within three months in the hundreds of cases he had treated up to then. Meanwhile, he had passed on from the original dose of 0·3 to 0·45 gramme for women, and 0·5 gramme for men. In a later report, August 11, 1910, on his 503 cases of disease treated with dioxydi-

amidoarsenobenzol, Wechselmann recorded three relapses; certainly only a very small portion of the cases treated had come to see him again. In the meanwhile, however, reports of various recurrences had come to hand from other sides after a preliminary injection of arsenobenzol. Thus, at a discussion held at the Göttinger Medical Society, on June 2, Schreiber and Hoppe stated they had seen relapses, and the reappearance of fresh specific efflorescences respectively, in ten cases within four weeks after 0·3 to 0·4 gramme of arsenobenzol. A. Neisser also reported various recurrences on June 30, 1910. He attributed these to the fact that the doses administered had been too small—viz., 0·4 gramme. Géronne and Huggenberg recorded that after observations extending over thirteen weeks they could testify to five relapses, amongst others "three men we had treated intramuscularly and intravenously respectively for primary ulcer. Here the clinical phenomena first disappeared surprisingly

rapidly, the Wassermann reaction became negative soon after the injection, and remained so for several weeks, and then, after seven to eight weeks, in place of the primary ulcer, a fresh erosion was formed, in which spirochætes could be detected. In these cases the Wassermann test had again become positive."

Hoffmann recorded relapses after an injection of the Ehrlich drug, and mentions that it is not uncommon to prove the presence of spirochætes in these relapses at a time when the Wassermann reaction is still perfectly negative.

On August 4, 1910, Bohač and Sobotka reported four relapses they had observed within a few weeks; 0·3 gramme had been injected. Neisser and Kusnitzki saw altogether five relapses, which they attributed to the fact that the doses administered had been too small. Loeb observed a recurrence, certainly after the application of a very small intravenous dose of 0·14 gramme. Ehrlich stated, in a communication on

August 12, 1910, that up to that day there had been about 4,000 cases under careful observation. He declared that in man complete recovery was possible with the new drug in 90 per cent. of the cases. This calculation was probably made, in consideration of the fact that up to that time there were only a small number of cases in which the clinical symptoms of specific disease had recurred.

According to a still later communication of Wechselmann's, the number of relapses, and partial failures respectively, out of the 900 cases he had treated up to the time of publication was small, almost down to vanishing-point; at any rate, "the number of the earlier recurrences remained far behind those of mercurial treatment." Wechselmann specially emphasises the insignificance of the relapses. Kromayer, Brändle, and Clingestein, out of twenty-seven cases, saw five relapses after two and a half to three weeks. Glück and Wolff observed four recurrences. Fischer re-

ported two severe relapses in patients treated by others with "Ehrlich-Hata," and in one extensive primary affection containing spirilla, which had been injected about eight weeks previously. Duhot saw a relapse in a patient who had been treated by another medical man with 0·3 gramme. Géronne saw fourteen relapses in about eighty syphilitic patients, who had been at least ten to twelve weeks under careful observation; he did not include in this summary the numerous patients who had been under observation for a shorter time. Eleven times there were reindurations of the primary affection, renewed appearance of a specific angina or of an exanthem; three patients got other similar specific symptoms. Denecke testified to the certain recurrence of an early tertiary ulcerous process. Ledermann, up to date, records a return of periostitic swelling of the cranium, which had completely disappeared with its symptoms, after an injection of 0·45 gramme; the appearance of roseola fourteen days after

involution of the primary affection (with 0·3 gramme), and two other relapses. Rille saw a recurrence of the primary affection about four weeks after cure. Weber observed two slight relapses, and Gennerich four in malignant syphilis after almost four weeks. In a recent communication, Schreiber put the total number of his relapses at sixteen after 0·3 and 0·4 gramme respectively; one recurrence after 0·7 gramme; he had no relapses after intravenous injection. Herxheimer also, in his last report of 230 cases, mentions two very slight local returns of secondary syphilis within four and a half months.

Linser, on the other hand, repeatedly noticed relapses in all stages, some of which occurred within four to six weeks of the injection. In Bering's observations, three recurrences of secondary syphilis appeared in his cases at the end of three to four weeks, despite the fact that the normal dose had been injected. In tertiary syphilis he registered a relapse at the end of four weeks.

Stern reported that in one of his cases of primary affection, with extensive exanthem, which had healed up by eighteen days after the application of "606," the exanthem having gradually retrogressed, there was a return of the papules on the thigh and of the mucous papules on the tongue and lip. Miekley observed two cases of relapse. In three cases of primary affection, Grouven was unable to prevent the appearance of the secondary phenomena, despite injections of 0·3, 0·4, and 0·5 gramme. He saw direct recurrences in a case of congenital syphilis (0·05 gramme), and in one of acquired specific disease (after 0·3 and 0·6 gramme). According to Friedländer, an injection of "Ehrlich-Hata" did not prevent the appearance of later secondary phenomena in three cases of primary affection. Joseph records one relapse after 0·3 gramme; Eitner two. I myself have had four certain relapses and two partial failures in the relatively small number of cases (twelve) I have treated with "606" (on an average, 0·6

gramme, partly in alkaline solution, partly in neutral calcium carbonate emulsion). In one of the cases which recurred after the prompt and rapid healing of two firm papules in both naso-labial folds, and in both angles of the mouth after 0·45 gramme of arsenobenzol, a new papule appeared at the left angle of the mouth, about fourteen days later, small plaques in the buccal mucous membrane, and a slightly indurated ulcer, covered with slime, in the sulcus coronarius. In the second case, a maculo-pustulous exanthem healed up completely within eight days. Fourteen days later this exanthem reappeared in an exaggerated form ; there was also an extensive impetiginous syphilide at the back of the head. These phenomena then disappeared completely after two to three injections of thymol acetin. With one patient, who had a hard infiltrated primary affection localised in a urinary fistula, and marked bilateral typical swelling of the lymphatic glands with large quantities of spirochætes and

isolated roseola, a distinct Herxheimer reaction set in on the day following the injection, which disappeared at the end of forty-eight hours. The infiltration of the primary affection had partially disappeared, as well as half of the left inguinal gland. Ten days after the injection, there was a sudden outbreak of numerous slightly infiltrated roseolæ on the upper part of the body and on the face. Finally, in the fourth case, one of latent specific disease with positive Wassermann reaction, papules appeared on the palmar eminences and on the arms four weeks after the injection of arsenobenzol. Urticarial roseola, with positive spirochæte result in some of the roseolæ, only healed partly ; slightly infiltrated and pigmented places still persisted. In one case the primary affection only healed up imperfectly, and a severe eruption of roseola soon appeared.

Apart from these certain relapses, however, there are a large number of other observations in which only a defective

action of the arsenobenzol on the syphilitic process could be proved.

In current literature such "failures" are generally recorded apart from the relapses, although the latter, in the opinion of Stern, must also be counted as "failures," and in this I thoroughly agree with him.

Wechselmann especially reports a whole number of such cases in his last publication, "The Reinjection of Dioxydiamidoarsenobenzol," in which a single injection of "Ehrlich-Hata" did not act as promptly and perfectly as Wechselmann had regularly observed previously. Thus, amongst others, infants suffering from pemphigus neonatorum, cases of severe malignant syphilis, which, it is true, were influenced in the most brilliant manner, but which still showed quite small ulcerations, and, further, an extensive papulous syphilide and a large flaked urticarial roseola, were all reinjected. In Wechselmann's experience, however, the number of partial failures, as contrasted with the number of prompt effects, is still

so small as to be almost at vanishing-point. Grouven and Fränkel were able to observe that sometimes the success of the treatment appeared much less rapidly. "In a facial papule two months after the first injection, a large number of mobile spirochætes were found. Another patient required three injections, extending over two months, to effect the disappearance of his tubero-serpiginous phenomena." Treupel observed a similar failure in a papule of the lower lip, which, it is true, reacted with redness and moisture, but did not become smaller. Glück saw thick papules and a primary affection uninfluenced at the end of three weeks. Hartung also did not always obtain satisfactory results in anal and genital papules. Iversen was unable to effect the cure of large papules within three weeks; Hoffmann found the action inadequate for an intense papulous syphilide, and had to supplement it by inunction treatment.

Pinkus stated that in two cases the secondary syphilitic papulous exanthem had

not disappeared at the end of four weeks (with 0·4 and 0·45 gramme); moreover, Spiethoff also records failures with these doses. Out of sixty-four cases of secondary syphilis, Bering five times saw the symptoms uninfluenced, although in some cases very high doses had been administered (0·8 gramme per kilogramme of the weight of the body). Scholtz recorded three failures with smaller doses of 0·3 to 0·4 gramme; in two cases of malignant syphilis, Géronne found that after 0·3 and 0·6 gramme, not only was there no cure, but a week later he discerned distinct deterioration. Here belongs also the case mentioned by W. Fischer of considerable exacerbation of tertiary ulcerous syphilis after an arsenobenzol injection. In eight cases, out of eighty treated with Ehrlich's "606" up to September 15, 1910, Stern could not speak of a noticeable rapid result, neither could Taege in the cases of a man with papules in his beard and of a woman with tumour of the liver. Volk and Lipschütz also saw two cases of atonic ulcers, which

were absolutely uninfluenced. Eitner also records four failures.

Quite recently the *Medizinische Klinik* started a fresh inquiry, in which the participators in the earlier one were asked to make additions to their contributions, with regard to the number of cases treated. I will here briefly recapitulate the contents of this inquiry, in order to complete and extend the report of the relapses and failures up to the present time, as far as possible.

Jadassohn treated eighty cases up to October 24. The relapse of one patient with *plaques muqueuses* was reported six weeks after he had had an injection of 0·5 gramme. A second patient was given 0·6 gramme arsenobenzol, and plaques were again evident five weeks later. In a third case, new papulous deposits appeared only twelve days after the injection of 0·6 gramme. Out of 789 cases, Herxheimer saw 33 relapses, Linser 4 out of 80. Spiethoff states that the number of cases he has treated amounts to 175; amongst them there

were 5 recurrences, 2 of which were observed after a second injection. Bering was able to make a later examination of 211 cases; amongst these he observed 25 failures, which equals 11·8 per cent. Pinkus, 120 cases, 3 relapses; Rille, 171 cases, 7 relapses; Treupel, 120 cases, 4 relapses; Juliusberg, 55 cases, and 2 recurrences and failures respectively. Grouven treated altogether 254 cases with arsenobenzol; 15 of these were failures in the sense that the symptoms only retrogressed lingeringly or imperfectly: 9 cases relapsed. Bettmann observed 8 relapses amongst the cases he had treated previously (87). Schultz, 1 recurrence out of 28 cases; McDonagh, 2 relapses out of 85 cases; Wechselmann, 40 out of 1,250 cases. "But the number is quite insignificant, as only a moderate percentage of those treated again presented themselves" (Wechselmann).

Amongst 120 cases of pure syphilis (not parasyphilitic diseases), L. Michaelis observed 4 relapses; up to the present

Kromayer has treated 310 patients, and 7 of these relapsed. "I may add," says Kromayer, "that the majority of the cases treated have not entered upon the stage when a recurrence may be anticipated, so that the numbers 310 and 7 cannot be placed in relation to each other." E. Saalfeld saw 5 relapses out of 36 cases; Halberstädter 6 out of 55; Ledermann also 6 out of 52; Chrzelitzer only 1 recurrence out of 47 cases. Gennerich was able to treat 82 cases; in 4 of malignant syphilis he had relapses at first, but later, in these cases also, by the aid of renewed injections, he was able to effect cures. Scholtz discovered 5 relapses out of 130 cases treated; Schreiber had 18 recurrences out of 152 cases which had been subjected to intramuscular injections, but there was only 1 relapse amongst 565 cases treated intravenously. Géronne reports that out of 71 patients with specific disease, who were injected between the months of April and June, 22 clinical recurrences had been

observed up to the present date; "24 of these patients were reinjected, on account of the persistence of the Wassermann reaction, by means of which the appearance of further clinical relapses was obviously prevented." Since the middle of August, Bruhns has treated 74 cases with Ehrlich-Hata "606"; up to now he has seen 5 relapses and 4 failures. Welander treated 65 cases altogether; but in his opinion this number also is without importance in estimating the relapses. The result of his arsenobenzol treatment is better indicated by the fact that, of his 46 adult patients, in all probability no relapse occurred in 27 cases. Welander also received notifications of the relapse of 11 adult patients; in 5 cases the symptoms were but little influenced. A recurrence was observed in the case of a child (hereditary syphilis), and with another the treatment failed. Von Zeissl saw 4 relapses out of 149 cases. Finally, Dreuw was able to observe 4 severe relapses amongst the cases of 11 prostitutes

subjected to police inspection, who had been treated elsewhere by Ehrlich-Hata injections. Polland and Knaur saw 4 recurrences in the secondary stage, and in one case an Ehrlich-Hata injection had not the slightest effect. Latterly, Wechselmann has observed severe eye trouble as a relapse.

Cohn has also reported an iritis relapse, which reappeared fourteen days after a prompt cure had been effected with "606." A probable specific neuritis of the optic nerve was seen by Kowalewski, in a secondary syphilitic woman, about two months after an Ehrlich-Hata injection. Fischer also testified to 5 severe cases of eye diseases out of 8 certain relapses.

Fischer is inclined to connect this form of relapse with the arsenobenzol treatment. He, like Buschke, believes the neurotropic affinity of this drug to a certain extent produces a *locus minoris resistentiæ*, on which the syphilitic virus fastens itself and finds a favourable field for development.

Wechselmann, who, as we have seen,

only observed the very slightest clinical relapses, believes that these "are only to be regarded as relapses of encapsulated foci, which have been made manifest under the action of the drug." "Our conception is that all the spirochætes which come in contact with the drug are destroyed, and probably softening processes take place at the infiltration foci, which harbour encapsulated spirochætes, and thus may make them accessible to the new drug." Wechselmann believes that the dose of 0·5 to 0·6 gramme for men, and 0·45 gramme for women, which has been found effective and generally adequate for cure, should not be exceeded.

In the circular letter of October 25, 1910, already referred to, Ehrlich attributes the appearance of relapses to the fact that the subcutaneous injection of neutral emulsions accomplishes less *quoad* duration of effect than other forms of application. It seems to him as though the *ictus immunisotoricus* in this method is not intense enough to generally obtain a destruction of the

spirochætes to the extent of sterilisation. As is known, it is for this reason that Ehrlich now hopes to be able to anticipate better results from the treatment with intravenous injections.

If, as is assumed by Ehrlich and a large number of syphilidologists, the positive or repeated negative result of the Wassermann reaction is a sure test as to whether the syphilis is healed up or not, then naturally amongst these clinical relapses and failures a large number of cases must also be reckoned, in which through a single and even repeated injection, the positive result of the sero-reaction was not lastingly transformed into a negative one.

In estimating the number of relapses of manifest specific symptoms detected by individual teachers, there are, in my opinion, still some important points to be taken into consideration.

In the first place, the statistics compiled by most authors from which they adduce and calculate the relapses are incorrect.

As has been claimed by Blaschko, not only must the stage of the disease be given accurately, but also how long the affection has been lying dormant in the cases treated. But, above all, the observation period is still far too short to enable one to formulate any definite conclusions with regard to the action of the arsenobenzol.

According to Alt's communication, the first attempts at treating florid syphilitic patients with "606" were begun on January 31, 1910. Wechselmann first received this preparation from Ehrlich in March, 1910, and most other teachers were only able to commence their therapeutic researches with arsenobenzol much later. Hence the longest observation period of syphilitic cases which have been subjected to this method of treatment, in the most favourable ones, is only a little over nine months, in many at most half a year, while in most of those cases reported up to the present, it is only a few months. We know, however, that in the so-called early

treatment of syphilis — excision of the primary affection, with subsequent intense mercurial treatment—with apparently complete cure, the appearance of recurrences or secondary symptoms may, under some circumstances, be delayed for above a year. I myself have had two observations of this kind, which I give. In one case, after excision of the primary affection and after three intense injection cures, it was eight months after the excision that pronounced roseola, with *impetigo capitis* and characteristic fall of hair, appeared (the Wassermann reaction had fluctuated equally between positive and negative). In the other case, the first hardly perceptible roseola showed itself about six months after the excision ; the second, which was not much more marked, about three months later.

It is evident from these observations that the course of specific disease may deviate from its typical curve, if the development of the syphilitic process is inhibited early, by means of drastic cures or strong specific

drugs. There is no doubt that Ehrlich's arsenobenzol is a preparation which has a strong specific action on syphilitic infected tissues of all kinds. Consequently, it is only possible to expect to be able to arrive at definite conclusions as to the possibility of a recurrence of the process of disease after at least twelve to eighteen months' careful observation of the cases thus treated.

A further fact, which must be taken into consideration, is that perhaps at the beginning, in conceivable enthusiasm over the good symptomatic effect of the new Ehrlich-Hata preparation, the results of the "cures" published were too rapid, and perhaps also too euphemistic. In the great interest which naturally was aroused by such publications, even the smallest report was referred to in detail in the daily press. Thus the public at large got the firm belief that it only required a single injection of Ehrlich-Hata "606" to render anyone exempt from syphilis for all time. This belief,

which to-day is still almost general, is the reason why most syphilitic patients who have been treated with "606" have not watched themselves, and their bodies respectively, with the greatest care for the appearance of any suspicious symptoms. Neither have they reported themselves to the medical man at regular intervals, as is always required to be done with mercurial therapy, even when there is apparently a complete absence of symptoms. This may have contributed to the reason why Wechselmann and many other teachers have seen so few of their patients again who had been treated with arsenobenzol. There is no reason why all these patients who failed to report themselves should have been cured. Indeed, it is just the fact that the manifest symptoms, under some circumstances, may be so slight that they are hardly perceptible, and often disappear surprisingly rapidly, even without specific treatment, which makes this disease such a terrible one, and so full of danger for the

general public. Apparently healthy patients, who are suffering from this disease in the latent stage, may occasionally spread infection if rapidly passing specific symptoms arise, which are often slight and unnoticed. I have unfortunately been able to convince myself of the possibility of this in one of the early cases described above, which I treated, in which a patient infected a girl with syphilis about two months before the outbreak of the general symptoms.

10. Secondary Effects.

In considering the question of the secondary effects to which this new preparation may give rise, we must, like Neisser, distinguish *purely local* disturbances, which appear at the seat of injection, and *general* secondary effects. As the former depend chiefly upon the manner of administering the drug, I have refrained from giving them until the different methods of solution and forms of application had been discussed.

Most teachers have expressed themselves as follows, with regard to the general secondary effects of the preparation "606" —namely, that these are comparatively of a very insignificant nature, and that arsenobenzol, even in larger doses, is relatively innocuous for the organism. Nevertheless, secondary effects have been seen on various sides, some of which were of a very grave kind, and these have made this innocuousness of the Ehrlich-Hata therapy appear in a somewhat different light. It is, however, important that the practitioner should be thoroughly acquainted with all these observations, and therefore they are given in detail here.

Fever is a regular symptom which appears after the administration of "606." In the majority of cases with intravenous injection it sets in with rigor a few hours after the injection, and runs up to 39·5° to 40° centigrade, but often falls within a few hours (Schreiber, A. Neisser, Géronne and Huggenberg, and Iversen). In intramuscular and

subcutaneous injections the fever generally begins one or even two days later, is not so high, and as a rule finally drops again. Schlesinger, however, observed high fever in one case for three weeks ; there was no local infection present. Neisser's observations show that no fever arises after the injection of non-syphilitic patients. He therefore regards fever after an arsenobenzol injection as a general reactionary phenomenon, and attributes it to the toxic action of the endotoxines liberated by the destruction of spirochætes. Very often phenomena of drug exanthemata accompany the appearance of fever. Thus, Wechselmann observed a morbillous exanthem with conjunctivitis. Spiethoff and Saalfeld also, twenty-four hours after the infection, saw an exudative confluent erythema of the extensor sides of the leg and thigh, with pain in the joints, which reminded one vividly of *exanthem exsudativum multiforme.* Twenty-four hours later it had ceased altogether. Fränkel, Rille and Grouven, and others,

perceived diffuse exanthemata, and true erythema respectively. In one case, six hours after the injection, Spatz was able to detect "elevated, irritating, bright red, nettle-rash-like infiltrations, varying in size from a crown to a five-crown piece," over the whole body and face, which again disappeared twenty-eight hours later, without leaving a trace behind. Herxheimer also noticed urticaria in one case, which began on the hands, and then gradually extended over the whole body. Glück also saw urticaria and exanthemata in some cases. Treupel once perceived a slight desquamation of the cutis of the face. Schreiber saw slight drug exanthem in two patients, which first appeared after eight to ten days, with rise of temperature, and then again disappeared rapidly. Finger was able to observe toxic erythema in four cases, amongst them being one similar to scarlatina, which arose with high temperature, and persisted for over a week.

Further, it is not unusual for the fever to

be accompanied by flatulence, nausea, retching (Alt, Kromayer, Rille, and Spiethoff), and in some cases with genuine vomiting (Wechselmann, Schreiber, Neisser, Iversen, Géronne, Rille, Gennerich, and von Zeissl). In intravenous injections especially, fever, vomiting, vertigo, and similar symptoms, were observed almost regularly, but as a rule they passed off equally quickly. The fever, however, is pretty frequently accompanied by acceleration of the pulse, tachycardia, and increase or diminution of the blood-pressure (Alt, Spiethoff, Schlesinger, etc.). Ledermann once saw pronounced slowing of the pulse. In my experience these symptoms may persist for a long time; indeed, up to fourteen days, while the temperature remains perfectly normal. The severest phenomena of the circulatory system, however, were seen by Hoffmann in two cases; in these were not only grave disturbances in the heart's activity, but also slight diffusion towards the right, and a systolic bruit after treatment. Hauck

also discovered marked disturbance in the heart's activity after a dose of 0·3 gramme.

Whether the Ehrlich drug is really so non-irritant for the kidneys, as has been asserted on various sides, is a question I must doubt after the experience of Schlesinger, who observed transitory albuminuria in about half the cases, or cylinduria without albumin. Bering also saw four cases of transitory albuminuria. Géronne records slight albuminuria in some cases, which, however, disappeared at the end of one to two days. The albuminuria was more pronounced in one case, and persisted four to five days; on the first day the albuminous content was 8 per cent., but there were neither cylinders nor red blood-corpuscles in the urine. Finger also observed a transitory albuminuria in one case. Volk and Lipschütz saw albumin and cylinders secreted from the urine eight days after one patient had had an injection. According to Pick, a frequently observed phenomenon is the diminution of the

quantity of urine, which in some cases has been reduced from 400 to 500 c.c. per day, when the specific gravity was not too high (1015 to 1020).

Slight isolated symptoms of disease of the intestinal tract have also been observed. Iversen saw transitory diarrhœa after intravenous injections; Bering reports intensely severe intestinal tenesmus, which lasted one or two days, in patients who had been treated with arsenobenzol. Pinkus saw transitory diarrhœa in one syphilitic patient, Schulz in two; Bettmann, Géronne, and Huggenberg also occasionally. Spatz mentions that the painful feeling of thirst, of which his patients complained particularly, occurred in cases in which the temperature did not exceed 37·5° centigrade, and hence could not be caused by fever. Bayet observed arsenical rheumatism, in many of the patients who had been treated with arsenobenzol, about fourteen days after the injection.

Distinctly graver symptoms were de-

scribed by Bohač and Sabotka in the three following cases. They observed :

" 1. Retention of urine, the duration of which varied, reaching to half a day. In one case, which could not be estimated at the time this work was concluded, it had certainly extended over a period of more than nine days ; after its cessation there was considerable difficulty in micturition left behind. It was surprising that, with patients who had been given the smallest amount of the preparation, very severe symptoms did not at once set in. In two cases there were also slight quantities of albumin in the urine, without cylinders.

" 2. The patellar reflex was absent in all the cases, as well as a whole series of reflexes which are usually tested. True, their condition conceivably had not been examined before the commencement of the treatment.

" 3. In two cases there was unusually marked tenesmus of the rectum (in one

case this was perhaps favoured by previous proctitis).

"Further, in all three cases intense constipation was noticeable, which still persisted after an abundant amount of nourishment was taken. Despite the fact that it was soon overcome by means of a simple aperient, this should perhaps not be confounded with the usual sluggishness of the bowels of anyone confined to bed."

The authors attributed the nervous symptoms to disturbances in the spinal cord, the rectal tenesmus to nervous irritation of the intestinal tract, and the retention of urine finally to detrusor paralysis. The authors are of opinion that this new arsenic preparation, as regards these symptoms, has points of contact with the secondary effects described as due to atoxyl. In contradistinction to this communication from Bohač and Sobotka, Privy Councillor Ehrlich has published the following declaration :

"FRANKFURT-A.-M.,
"*August* 1, 1910.

"With regard to the article by Bohač and Sobotka, I may remark that 132 additional tubes with the same operative number as those employed in Prague were sent to Fauser (Stuttgart), Hauck (Erlangen), Linser (Tübingen), Rille (Leipzig), and Spiethoff (Jena). From all these places I have received reports to the effect that the disturbances described by the authors were never observed. Moreover, nothing of the kind has been reported to me from elsewhere in the administration of '606.'

"On inquiry, Alt (Uchtspringe) telegraphed to me: 'In more than 200 cases which were treated with "606" in the Institution here, under the most exact control and careful examination, especially with regard to the nervous system, nothing similar to what occurred in Prague has been observed. There has never been any paralysis of the bladder, retention of urine, or the like, nor any disappearance of the

reflexes. There must, therefore, have been some toxic action which was brought about, either by decomposition of the preparation or by the addition perhaps of methyl-alcohol. I employ no basic additions, with the exception of a little solution of caustic soda.'

"Dörr (Vienna) telegraphed also on my inquiry: 'Sixty-eight cases, no paralysis of bladder; reflexes tested day before yesterday by neurologists in all accessible patients; not absent in a single one.'

"Similar telegrams were received from Finger (Vienna) of forty cases, Neisser (Breslau) of 110, Michaelis (Berlin) of sixty-eight.

"It is evident from the above that the disturbances observed by the authors were connected neither with the preparation '606' itself nor with any decomposition of the special operative numbers. There must, therefore, have been sources of error in the preparation of the solution or in the application. According to telegraphic news received from Sellei (Budapest), 'Kreibich's failures are typical symptoms of methyl-

alcoholic intoxication.' This also agrees with Alt's telegram and earlier communications from Aulic Councillor Emil von Gross (Budapest) ; they must have been due to an injurious effect of methyl-alcohol, which was perhaps not quite pure.

" In conclusion, I must express my regret that the authors did not consider it necessary to at once inform me of this occurrence, as then the sensational disturbance of a large circle, which was caused by the article, would have been prevented.

" EHRLICH."

In a second report on the further course of these cases, Bohač and Sobotka state that the longest duration of the complete retention of urine was ten days, that of tenesmus a little more. The disturbances of the patellar reflexes, which, together with the remaining reflexes, had been re-established in the meanwhile, might, in the opinion of the authors, be explained as the influence of pain starting from the seat of

injection, in the sense of a voluntary or involuntary inhibition. For the remainder of the secondary effects observed, however, this circumstance could not be taken into consideration. Neither, in the opinion of the authors, could these unpleasant secondary effects be attributed to a toxic action of the methyl-alcohol, as previously, in many cases in which methyl-alcohol had been employed for the preparation of the solution of arsenobenzol, no similar effect had been observed. Further, Ehrlich himself expressed the opinion (*Münch. Med. Wochenschrift*, 1910, p. 1576) that no objection could be raised to the employment of methyl-alcohol in such small quantities as come into consideration here. The authors believe that the explanation of this toxic action is due to the fact that the preparation in question had undergone a chemical change and was decomposed. This view is shared by Eitner, who quite recently was able to observe similar symptoms in one case—retention of urine, constipation,

absence of patellar and other reflexes. Buschke and his assistant Fischer, however, regard this action, like those they themselves observed, and which are given below, as well as many reports published previously, as being due to the neurotropic action of the arsenobenzol.

Another thing, which perhaps speaks in favour of the possibility of a neurotropic action in Buschke's sense, is the fact that slight relapses occur in the eyes and organs of hearing particularly, and to this I have already referred.

Latterly, Finger has reported some observations, and these directly confirm the assumption of Buschke. In one of these cases, a patient developed violent headache, vertigo, and optic disturbances two months after a Hata injection of 0·45 gramme. Objective examination revealed oculomotoric paresis on the right side, paralysis of the levator palpebræ superioris and of the rectus internus, as well as commencing optical neuritis of the left side. As it was

assumed that this was perhaps due to a relapse, the patient was given a fresh Hata injection also of 0·45 gramme. Nevertheless, this, as well as mercurial and iodine treatment, remained not only unsuccessful, but optical neuritis of the right side set in. With a second patient, optical disturbances set in three months after the injection, and were characterised by abducens paralysis. In a third similar case which Finger observed, the patient complained of optical disturbances three months after an injection of 0·45 gramme. On examination, it was found that there was sluggish reaction of the pupils, anisocoria, bilateral contraction of the visual field, retraction of the temporal halves of both pupils, therefore, commencing bilateral optical atrophy. Finally, in the fourth case, three months after the injection and eight after infection, optical disturbances were perceived, and right ocular peripheral chorioiditis, with central vitreous opacity. In three further cases "peculiar phenomena, partly of a disturbing nature,"

were found in the auditory organ.[1] Once Finger saw isolated interruption of the vestibular nerves, although certainly this was only transitory. In another case, a patient complained of vertigo and difficulty in hearing nine weeks after the injection and three months after infection. There was bilateral labyrinthal difficulty of hearing, which subsequently remained unchanged. In the third case, the patient, a girl, aged eighteen, with specific disease of about three months' standing, had been given 0·45 gramme arsenobenzol on August 5. By August 15, all syphilitic symptoms had disappeared, and the patient was discharged as cured. On November 7, she returned on account of giddiness, headache, and difficulty in hearing ; she was free from syphilis, and the Wassermann reaction was negative. Here also labyrinthal difficulty of hearing, vertigo, and spontaneous nystagmus, were detected, and later the condition remained stationary.

[1] Compare the secondary effects of Arsacetin, p. 27

Distinct confirmation of the experience of Bohač and Sobotka was obtained in the communications of Bonhöffer, who, in the case of one patient with fresh spinal syphilis, after an injection of a neutral emulsion, observed complete paralysis of the bladder, and an augmentation of the paralytic symptoms in the legs. With a second patient, a paralytic, he witnessed a severe epileptic attack, with residuary bilateral hemianopsy, etc. According to Pollack and Kaur, with one patient who had had 0·5 gramme, fever up to 40·1° centigrade set in, with strong acceleration of the pulse and retention of urine, which persisted for seven days. Rille also once observed an epileptic attack and repeated pain in the knees and legs. Schlesinger several times testified to transitory vesical disturbances in his patients. Herxheimer had a case of retention of urine; and even Wechselmann found that for a time one patient was incapable of emptying the bladder. Behring also once saw detrusor

paralysis. Chrzelitzer discovered arsenic intoxication in patients with excessive nervous disturbances, and Wechselmann, Pick, Fischer, and Buschke were able to prove the presence of slight arsenicism in isolated cases. In Wechselmann's wards three cases of paralysis of the peroneus were observed after intramuscular application. In the opinion of Sieskind, these cases are to be attributed to the mode of application, because the peroneus, from its superficial position, suffers external injury far oftener than the tibial fibres of the sciatic nerve. Now, as these cases of paralysis appeared after a latent period of a few days, Wechselmann regards them as arsenic intoxication neuritis proceeding from a deposit. Here probably we have to do principally with the effect of pressure of the intragluteal injection. According to Buschke and Fischer, it is possible that they may be explained as paralysis of the extensors, and thus as a symptom of an existing arsenic intoxication. That under

some circumstances the internal organs can also be injured is proved by a case of Hoffmann's, in which, after the injection of 0·3 gramme arsenobenzol in acid[1] solution, he saw central embolic pneumonia through escaped thrombus from the gluteal muscles. Finger once perceived symptoms of slight pulmonary embolism after an injection of a paraffin emulsion into the gluteus. Duhot three times observed hæmorrhagic excrescences. Rille saw dyspnœa and icterus thrice. Pinkus also was once able to testify to icterus after the administration of the Ehrlich-Hata preparation "606," and Behring to augmentation of existing diabetes. That occasionally pregnant women do not tolerate the new Ehrlich drug as well as Wechselmann and others assume, is shown by the observations of Loeb and Glück, each of whom observed an abortion after the injection.

[1] As is known, Alt, Schreiber, and Hoppe warn practitioners most emphatically against the injection of acid solutions.

The practitioner is naturally particularly interested in the communications of fatal cases which have occurred after injections of arsenobenzol, and, respectively, whether these could be connected with the preparation either directly or indirectly.

Wechselmann himself had three infants with pemphigus neonatorum, who were treated with "606," and died after fever, anæmia, and in one case opisthotonus, had set in. Herzheimer also reported two such cases of the deaths of syphilitic infants. As I have already stated, Wechselmann explains these fatal cases as the effect on the weak infantile organism of the endotoxines, which have been liberated by the destruction of large quantities of spirochætes. Schreiber and Hoppe record two fatal cases in adults, which, in the opinion of the authors, were not connected with the treatment. Iversen reports a fatal case in a woman who relapsed after a dose of 0·3 gramme. Acute nephritis, with hæmorrhagic exanthem, set in, and the post-mortem revealed arterio-

sclerosis, myocarditis, and other excessive changes, which already existed in the vitally important organs. In a patient who had been ill for years, with severe disturbances of speech, auditory aphasia, etc., on a syphilitic basis, Fränkel and Grouven experienced typical arsenical intoxication. This occurred a quarter of an hour after an intravenous injection of 0·4 gramme arsenobenzol diluted with 15 c.c. water, and the patient succumbed three and a half hours later. Hoffmann mentions a case of death after 0·3 gramme "606" in acid solution, and Spiethoff a further one after 0·5 gramme in a badly nourished, anæmic person. Orth showed preparations from two cases of necrosis of the gluteal muscles, after an injection of "606," at the Königsberg Meeting of Natural Philosophers. In one of the cases, death had occurred ten days after the injection; in the other, the fatal issue had been caused by a pharyngo-laryngeal carcinoma.

Quite recently details of a fatal case were

reported by Ehler. This occurred in August, 1910, subsequent to an injection of 50 centigrammes "606," under increasing symptoms of intoxication exclusively of the nervous system (tremor, shivering, attacks of perspiration, loss of power, etc.). True, the patient in question was paralytic, and had already suffered from two apoplectic attacks. "Nevertheless, before he came under treatment with '606,' he could vegetate, walk, read the newspapers, and understand various things in them." Post-mortem revealed no other cause of death beyond acute parenchymatosic degeneration of the organs.

With regard to these fatal cases, Ehrlich expresses himself as follows :

"Out of a large number of cases, only one fatal one has been observed (at Jena) which concerns a patient, who would not have succumbed to the disease in any event. She was a weakly person, with tertiary syphilis of the larynx, to whom, for external reasons, an injection of an acid solution

was given, a solution which has a particularly strong local irritant effect. I believe, therefore, that in this case death was due to the effect of shock, which I hope I shall be able to avoid in future with the new methods of administration."

The other groups of fatal cases, which hardly reach a dozen, concern patients exclusively with severe affections of the nervous system—such as tabes with cystitis and cachexia with bulbar symptoms; further, patients with extensive cortical softening, and similar cases. In one of these, microscopic examination gave the following result, which I repeat word for word:

"In the case of the dead patient, microscopic examination showed that at the seat of the exit of the phrenic nerve from the upper cervical spinal cord, the anterior roots were embedded in diseased (infiltrated) tissue, and showed slight degenerative changes. It is quite possible that, in consequence of the reaction, irritant or swollen conditions (œdema ?) may have been

induced by compression of the phrenic nerve which was already slightly diseased, and resulted in sudden respiratory paralysis.

"Now, granting that this case in itself is grievous, I believe that its chief importance is that it shows the greatest caution is necessary in administering '606' in syphilitic diseases of the upper cervical spinal cord. Unfortunately, as in our case, it is not always possible to diagnose these diseases with certainty."

It is evident, from the communications on the secondary effects of arsenobenzol detailed above, that a certain organotropic action may also be attached to this preparation, which occasionally leads to extremely unpleasant organic disturbances. The toxic action of arsenobenzol on the facial and auditory nerves, which Finger observed, unfortunately gives rise to the conviction that arsenobenzol, under some circumstances, may have a very injurious toxic effect on the nerves, although to a slighter extent than atoxyl and arsacetin.

II. Epicrisis.

There is no doubt that a great advance in the therapy of syphilis is marked by the introduction of organic arsenic preparations into specific therapy by Uhlenhuth, and especially by Ehrlich's discovery of dioxydiamidoarsenobenzol.

For, on the one hand, the new Ehrlich-Hata preparation "606" — *i.e.*, arsenobenzol—appears, from evidence before us up to the present, to be at least less toxic than other similar arsenic preparations, and, on the other hand, with regard to its generally prompt and rapid action on manifest syphilitic symptoms, to surpass mercury in many cases. Even if, as the numerous relapses teach us, in the doses and application up to the present, a *sterilisatio magna* of the organism has certainly not been obtained in the way Ehrlich imagines, and in such a chronic and complicated disease as human syphilis certainly cannot be obtained (Uhlenhuth); still we must

acknowledge that arsenobenzol forms a valuable drug for us medical men in the treatment of syphilis. True, some time must still elapse, and much experience must be collected and questions explained, before we learn to employ the new remedy correctly and appropriately.

By means of summarising the reports on the subject before us, which have been kept as objective as possible, I think the practitioner will be in a position to judge for himself when, and respectively in what cases, he may make use of the new Ehrlich-Hata drug, how he has to administer it, and what result he may hope to obtain.

With the apparently relatively slight toxic action of arsenobenzol, the practitioner will certainly be able to employ this new preparation in all stages of syphilis. He must use it in cases which are refractory to mercurial and iodine therapy, or which have been but little influenced by them. Fortunately, in nearly all similar cases, arsenobenzol exercises a particularly good

and satisfactory action. Further, it has been observed in such cases that, after an injection of arsenobenzol, mercury has again had a more favourable effect on any residue that still persists. This is also the case in forms of the disease, especially of the tertiary, malignant, and ulcerous tertiary periods respectively, and of hereditary syphilis, in which a single dose of "606" may often practically have a life-saving effect. In far-advanced para- and meta-syphilitic diseases of the nervous and vascular systems, it is well, as Ehrlich recommends, to abstain from the administration of arsenobenzol in general. For, in the first place, opinions are in agreement that here one may expect the least success, and, especially in advanced cases, this drug may under some circumstances have a very toxic effect.

Further, arsenobenzol should be employed if frequent relapses occur a short time after a mercurial cure. If regular cases of fresh syphilis of the primary and secondary

periods are treated with arsenobenzol, somewhat from the standpoint of being able to exercise a preventative or arresting effect respectively, as in early treatment, then, as is advised by Hoffmann, Neisser, Weintraub, and others, it will be necessary, under all circumstances, to follow this up with a few drastic mercurial treatments. For it is not merely the manifest phenomena of syphilis we are treating, and of which respectively we wish to effect the disappearance. Even if these had healed up a short time after the beginning of the specific cure, we continued the treatment for a certain time. Indeed, we repeated whole cures even if the patients were free from symptoms, "as" (I quote from the words of W. Fischer) "experience has taught us to regard prolonged mercurial therapy as a certain prophylaxis against further relapses and deleterious secondary diseases." Whether we may hope for the fulfilment of these expectations with arsenic preparations also, and especially with Ehrlich's

arsenobenzol, remains to be seen from the experience of many years.

In considering whether we should employ arsenobenzol in the treatment of primary and secondary syphilis, we must further be influenced by the question whether we have actually in the Ehrlich-Hata preparation one which is superior to mercury, and is at the same time less toxic. We know that certain cases of the primary and secondary periods, such as large markedly indurated primary affections, severe glandular swellings, papulous exanthemata, and anal and genital papules, are less accessible to the new preparation than to the usual mercurial therapy. Further, most of the failures and relapses respectively, which have been observed up to the present, have been especially in the early secondary period. With a few injections, however, of one of the usual mercurial preparations, we mostly attain the same object. Further, these have not such unpleasant, and indeed toxic, secondary effects, as may sometimes, under

some circumstances, follow an injection of arsenobenzol.

In any case, patients who have been treated with arsenobenzol in the early period of syphilis must be kept under careful supervision, even after the disappearance of the manifest symptoms. The present condition of their disease must be explained to them—*i.e.*, the possibility of the appearance of relapses and the power of transmitting infection in the latent period—and above all they must be warned not to marry too soon or incautiously, or again resume sexual intercourse. I have already mentioned in discussing relapses that, in consequence of the extremely favourable first reports of the Ehrlich-Hata "606," the idea has penetrated into all lay circles, "Cure of syphilis at one stroke," and an explanation without reserve is imperative in the interest of universal welfare.

Now, as regards the contra-indications to treatment with arsenobenzol, in the first

place, advanced diseases of the nervous and vascular symptoms belong here. Completely compensated heart troubles, according to Grassmann, do not require to be excluded from Ehrlich - Hata treatment without further question. Naturally, great caution is necessary when other organic diseases are already present, especially of the kidneys, even when it is a question of direct syphilitic diseases of these organs. As I have already mentioned, arsenobenzol should not be applied without hesitation to diseases of the optic nerves, even if these rest on a syphilitic basis, having regard to the nature of this preparation.

Further questions, such as whether we know the highest innocuous dose for the individual injections properly, whether and within what intervals of time the injections should be repeated, and to what total dose we dare go without injuring the organism, are, as I also mentioned above, not yet fully explained at the present time.

Various authors repeat the injections in the event of the action being unsatisfactory, or in relapses, once to twice within shorter or longer intervals, generally in somewhat smaller doses than at the first injection. Up to the present, no specially toxic secondary effects have been observed with these repeated injections, but the cause of the disease has not always disappeared altogether. In the occasional repetition of the injections, the practitioner must exercise great caution, and must always take into consideration that if there is any deposit of arsenic present—such as are formed by intramuscular and subcutaneous injections, and can persist for a fairly long time—a cumulative arsenic action may easily be set up. Von Raven cautions practitioners regarding the frequent repetition of small doses, especially of arsenophenylglycin, which is so closely related to arsenobenzol, because this may bring about hypersensibility, and have a toxic effect. Whether, however, the repeated injection of

arsenobenzol, as of atoxyl, may give rise to serious injury, especially of the optic nerves, is, in my opinion, not yet sufficiently determined to permit of a general repetition of the Ehrlich-Hata drug.

At the conclusion of my work, I must not neglect to express my sincerest thanks to my highly-esteemed chief, Privy Counsellor Uhlenhuth, Director of the Imperial Health Bureau, and to my much-respected colleague, Dr. Arndt, First Assistant of the Imperial University Polyclinique for Skin and Venereal Diseases, Berlin, for their kind assistance.

LITERATURE[1]

ALT: "Tentative Treatment of Paralytics with Arsenophenylglycin." *Münchener Med. Wochenschr.*, 1909, No. 29, p. 1457.

—— "The Newest Ehrlich-Hata Preparation for Syphilis." *Ibid.*, 1910, No. 11, p. 561.

—— "On the Technique of the Treatment with the Ehrlich-Hata Syphilitic Drug." *Ibid.*, 1910, No. 34, p. 1774.

—— *Berliner Klin. Wochenschr.*, 1910, No. 27, p. 1293.

—— *Ibid.*, 1910, No. 40, p. 1857.

—— "The Significance of the Newest Treatment of Syphilis for Public Hygiene." *Zeitschr. f. Medizinalbeamte*, 1910, No. 14.

—— Remarks made during discussion at the Eighty-Second Meeting of German Natural Philosophers at Königsberg. *Deutsche Med. Wochenschr.*, 1910, No. 41, p. 1896.

ASSMY: "On the Technique of Intravenous Hata Injections." *Med. Klin.*, 1910, No. 48, p. 1898.

BASCH: *Budapesti Orvosi Ujság*, 1910, No. 37.

—— Berliner Med. Gesellschaft, *Therap. d. Gegenw.*, 1910, No. 7.

[1] Up to the beginning of December, 1910.

BERTARELLI, PASINI, BOTELLI: *Giornale italiano delle malattie venerée e della pelle*, 1910, No. 4.

BLASCHKO: Report of the German Society for the Combating of Venereal Diseases, 1910, viii., No. 4.

—— "Critical Observations on the Ehrlich-Hata Treatment." *Berliner Klin. Wochenschr.*, 1910, No. 35, p. 1611.

BLUMENTHAL: *Med. Woche.*, 1902, No. 15.

—— *Med. Klin.*, 1907, No. 12.

—— AND JACOBI, *Therapeut. Monatshefte*, July, 1907, and *Deutsche Med. Wochenschr.*, 1907, No. 26.

BIRINGER: *Therapeut. Monatshefte*, August, 1903.

BOHAČ AND SOBOTKA: "On Undesirable Secondary Effects after the Employment of Dioxydiamidoarsenobenzol ('606' Ehrlich-Hata"). *Wiener Klin. Wochenschr.*, 1910, No. 30, p. 1102.

—— —— "Appendix to the Communication on Undesirable Secondary Effects after the Employment of Dioxydiamidoarsenobenzol ('606' Ehrlich-Hata"). *Ibid.*, 1910, No. 31.

—— —— "Remarks on Ehrlich's Reply, 'On Vesicular Disturbances after the Employment of the Preparation "606"' in No. 30 of this Journal." *Ibid.*, 1910, No. 34, p. 1224.

BORNEMANN: *Münchener Med. Wochenschr.*, 1905, No. 22.

BRÄNDLE AND CLINGESTEIN: "Results up till now with Ehrlich '606.'" *Med. Klin.*, 1910, No. 34, p. 1332.

BREINL AND TODD: *Brit. Med. Journ.*, 1907, i. 19.

BRESSLER: "The Treatment of Syphilis with the Ehrlich-Hata Drug (Dioxydiamidoarsenobenzol)." First to Third Editions, Halle-am-Saale.

BREUNING : *Derm. Zentralbl.*, x., No. 5.

CITRON, H., AND MULZER, P : " On the Preparation of Ready-Made Solutions of Dioxydiamidoarsenobenzol (Ehrlich-Hata '606')." *Med. Klin.*, 1910, No. 39, p. 1531.

DARRIER : *La Clinique ophthalmologique*, 1907, No. 3.

DOBROVITS : " On the Curative Effect of Ehrlich '606' on the Infant through the Mother." *Wiener Med. Wochenschr.*, 1910, No. 38, p. 2209.

—— *Ibid.*, 1910, No. 40.

DONAGH, Mc : *Lancet*, ii., No. 10, 1910.

DÖRR : *Wiener Klin. Wochenschr.*, 1910, No. 26, p. 987.

DUHOT : *Annales de la Polyclinique centrale*, Brussels, 1910, Nos. 5 and 6.

—— " 606." Published by the Brussels Central Polyclinique.

—— " Unexpected Results in an Infant with Hereditary Syphilis after treating the Mother with '606.'" *Münchener Med. Wochenschr.*, 1910, No. 35, p. 1825.

EHRLICH : " On the Present Position of Chemotherapy." *Berichte der Chem. Gesellsch.*, xlii., No 1.

—— " Chemotherapy of Infectious Diseases." *Zeitschr. f. ärztl. Fortbildung*, 1909, vol. vi., No. 23, p. 721.

—— " Chemotherapeutical Trypanosome Studies." *Berliner Klin. Wochenschr.*, 1907, Nos. 9-12.

—— " On Vesicular Disturbances after the Employment of the Preparation '606.' Reply to the Article," etc. *Wiener Klin. Wochenschr.*, 1910, No. 31, p. 1132.

—— *Med. Klin.*, 1910, No. 34, p. 1322.

EHRLICH: "Does the Intravenous Injection of '606' present any Special Dangers?" *Münchener Med. Wochenschr.*, 1910, No. 35, p. 1826.

—— "Chemotherapy of Infectious Diseases." *Zeitschr. f. ärztl. Fortbildung*, vol. vi., No. 23, p. 721.

—— AND BERTHEIM: *Pharm. Ztg.*, 1907, May 1.

—— —— *Berichte der Deutsch. Chem. Gesellschaft*, xl., 3293.

—— AND HATA: "The Experimental Chemotherapy of Spirilloses." Published by Julius Springer, Berlin, 1910. English Translation, Rebman Limited, 1911.

EHRMANN: "Some Remarks on the Action of the New Ehrlich Preparation '606.'" *Wiener Med. Klin.*, 1910, No. 38, p. 2202.

EITNER, E.: "Collection of Illustrative Cases of Ehrlich '606.'" *Wiener Klin. Wochenschr.*, 1910, No. 34, p. 1233.

—— "Vesicular Disturbances and Other Secondary Effects after an Injection of Ehrlich '606.'" *Münchener Med. Wochenschr.*, 1910, No. 45, p. 2345.

EMERY: "The Preparation '606.'" Paris, 1910, No. 37.

—— "The Treatment of Syphilis with the Ehrlich Preparation '606.'" Proceedings of the Eighty-Second Meeting of German Natural Philosophers and Physicians at Königsberg, on September 20, 1910. *Deutsche Med. Wochenschr.*, 1910, No. 41.

FAUSER: *Med. Korrespondenzbl. d. Württ. ärztl. Landesvereins*, July, 1910.

FAVENTO : *Münchener Med. Wochenschr*, 1910, No. 40, p. 2080.

FINGER : *Ärztl. Reform-Ztg.*, 1910, No. 14.

—— "The Newest Stimulants in the Domain of Syphilidology." *Wiener Klin. Wochenschr.*, 1908, No. 1, p. 1.

—— "The Treatment of Syphilis with Ehrlich's Arsenobenzol." *Ibid.*, 1910, No. 47, p. 1667.

FISCHER, W. : "On the Ehrlich Treatment of Syphilis." *Therapie d. Gegenwart*, September, 1910, No. 9.

—— "Contributions to the Treatment of Syphilis with Ehrlich-Hata '606.'" *Med. Klin.*, 1910, No. 45.

—— AND HOPPE : "The Behaviour of the Ehrlich-Hata Preparation in the Human Body." *Münchener Med. Wochenschr.*, 1910, No. 29, p. 1531.

FLECKSEDER : *Wiener Klin. Wochenschr.*, 1910, No. 36, p. 1279.

FORBAT : *Ibid.*, 1910, No. 40.

FRÄNKEL AND GROUVEN : "Practice with the Ehrlich Drug '606.'" *Münchener Med. Wochenschr.*, 1910, No. 34, p. 1771.

FULD : *Semaine Médicale*, 1910, No. 38.

FÜRTH : "Practice with Ehrlich '606.'" *Wiener Klin. Wochenschr.*, 1910, No. 43, p. 1524.

GALEWSKY : Reference, *Med. Klin.*, 1910, No. 47, p. 1877.

GENNERICH : "On the Treatment of Syphilis with Ehrlich '606.'" *Berliner Klin. Wochenschr.*, 1910, No. 38, p. 1785.

—— "Observations as to Place of Application and Dosage with Ehrlich's Treatment." *Ibid.*, 1910, No. 46, p. 2089.

GENNERICH: "On the Treatment of Syphilis with Ehrlich '606.'" *Berliner Klin. Wochenschr.*, 1910, No. 1735.

GERBER: "On the Effect of the Ehrlich-Hata Drug '606' on Spirochætes of the Mouth." *Deutsche Med. Wochenschr.*, 1910, No. 46, p. 2144.

GÉRONNE AND HUGGENBERG: Reports from the Wiesbaden Medical Society. *Berliner Klin. Wochenschr.*, 1910, No. 28.

GLASER: "Ehrlich '606.'" Editions 1-3, Vienna, 1910.

GLAUBERMANN: *Berliner Klin. Wochenschr.*, 1907, No. 36.

GLÜCK: "A Short Account of 109 Cases of Syphilis treated with '606.'" *Münchener Med. Wochenschr.*, 1910, No. 31, p. 1638.

GOURWITSCH AND BORMANN: "The Ehrlich-Hata Preparation '606.'" *Deutsche Med. Wochenschr.*, 1910, No. 38, p. 1750.

GRASSMANN: "Which Heart Diseases form a Special Contra-indication to the Employment of Ehrlich-Hata '606'?" *Münchener Med. Wochenschr.*, 1910, No. 42, p. 2178.

GREVEN: *Ibid.*, 1910, No. 40.

GRÓSZ: "Arsenobenzol (Ehrlich '606') in Syphilitic Diseases of the Eyes." *Deutsche Med. Wochenschr.*, 1910, No. 37, p. 1693.

GRÜTER: "Arsenobenzol in External Diseases of the Eyes." *Ibid.*, 1909, No. 10, p. 444.

HALLOPEAU: *Bulletin général de Thérapeutique*, June 23, 1907.

—— AND BOUDET: *Bulletin de Dermatologie et de Syphiligraphie*, 1907, No. 6.

HALLOPEAU: *La Clinique*, September 6, 1907

—— "On an Abortive Treatment of Syphilis in Thirty Days." *Bulletin de l'Académie de Médecine*, Third Series, vol. lxiii., p. 482.

HAMEL, H.: "The Treatment of Syphilide by Means of Local Mercurial Injections." *Annales de Derm. et de Syph.*, May, 1908.

HECKER: "Estimation of the Efficacy of Ehrlich-Hata '606.'" *Deutsche Med. Wochenschr.*, 1910, No. 46, p. 2143.

HEINRICH: "Some Noteworthy Cases of Arsacetin Treatment, with Historic and Critical Remarks." *Therap. Monatsh.*, 1910, November number.

HENIUS: Inaugural Dissertation. Giessen, 1902.

HERMANN: "Some Remarks on the Effect of the New Ehrlich Preparation '606.'" *Wiener Med. Wochenschr.*, 1910, No. 38, p. 2202.

HERXHEIMER: "Arsenobenzol and Syphilis." *Deut. Med. Wochenschr.*, 1910, No. 33, p. 1517.

—— G., AND REINKE, F.: "On the Influence of the Ehrlich-Hata Drug on the Spirochætes in Congenital Syphilis."

—— AND SCHONNEFELD, *Med. Klin.*, 1910, No. 36, p. 1400.

HEUBER: *Therap. Monatsch.*, 1910, No. 8.

HEUCK: *Berliner Klin. Wochenschr.*, 1907, No. 35.

HEYMANN: *Deutsche Med. Wochenschr.*, 1909, No. 50.

HOCHE: *Münchener Med. Wochenschr.*, 1905, No. 14.

HOFFMANN, E.: "Appendix to the Work of Schaudinn and E. Hoffmann on *Spirochæta pallida*," etc. *Berliner Klin. Wochenschr.*, 1905, No. 23.

HOFFMANN, E.: "Upon the Presence of Spirochætes in Ulcerous Carcinoma." *Berliner Klin. Wochenschr.*, 1905, No. 28, p. 880.

—— "Further Communications on the Presence of *Spirochæta pallida* in Syphilis." *Ibid.*, 1905, No. 32.

—— "*Spirochæta pallida* in a Macaque inoculated with Blood." *Ibid.*, 1905, p. 46.

—— "Further Communications on the *Spirochæta pallida*, with Demonstration." *Derm. Zeitschr.*, 1905.

—— "On the *Spirochæta pallida*." *Deutsche Med. Wochenschr.*, No. 43, p. 1710.

—— "The Ætiology of Syphilis," Julius Springer, Berlin, 1906.

—— "Atlas of Ætiological and Experimental Syphilitic Research." Julius Springer, Berlin, 1908.

—— AND BLUMENTHAL: "Estimate of Sero-diagnosis in Syphilis." *Derm. Zeitschr.*, 1908, p. 23.

—— "The Ætiology of Syphilis." Published by Julius Springer, Berlin, 1910.

—— "The Treatment of Syphilis with the New Ehrlich-Hata Arsenic Preparation." *Med. Klin.*, 1910, No. 33, p. 1291.

HOLLÄNDER: Society of Internal Medicine (Meeting of July 1, 1907). Reference in *Berliner Klin. Wochenschr.*, 1907, No. 30, p. 974.

HÜGEL AND RUETE: *Münchener Klin. Wochenschr.*, 1910, No. 39.

IGERHEIMER: *Berliner Klin. Wochenschr.*, 1910, No. 33.

ISAAC, B. : "Results with the Ehrlich Preparation '606' (Dioxydiamidoarsenobenzol)." *Berliner Klin. Wochenschr.*, 1910, No. 33, p. 1528.

IVERSEN : "On the Effect of Ehrlich's New Arsenic Preparation ('606') in Relapsing Fever." *Münchener Med. Wochenschr.*, 1910, No. 15, p. 777.

—— "On the Treatment of Syphilis with Ehrlich's Preparation '606.'" *Ibid.*, 1910, No. 33, p. 1723.

JARAUX : *Presse Méd. Belge*, 1910, No. 37.

JOHNSTON, A. : "Intravenous Injection of Soamin in Cerebrospinal Meningitis." *Brit. Med. Journ.*, 1910, vol. i., p. 193.

JUNKERMANN : *Med. Klin.*, 1910, No. 35.

—— "On the Technique of Treatment with the Ehrlich Preparation '606.'" *Ibid.*, 1910, No. 40, p. 1572.

JUTOCH, MC : *Lancet*, ii., No. 10, 1910.

JVANYI : *Wiener Med. Wochenschr.*; 1910, No. 36.

KALB : "On the Action of Ehrlich's Arsenobenzol on Syphilis of Children, with Special Reference to Congenital Syphilis." *Ibid.*, 1910, No. 39, p. 1378.

KLEMPERER : "On the Treatment of Pernicious Anæmia." *Berliner Klin. Wochenschr.*, 1908, No. 52, p. 2293.

KOWALEWSKI : "Neuritis Optica as a Relapse after Ehrlich-Hata ('606')." *Ibid.*, 1910, No. 47, p. 2141.

KREN : "On the Treatment of Syphilis with Ehrlich's Remedy." *Wiener Klin. Wochenschr.*, 1910, No. 45, p. 1596.

KOCH, R.: *Deutsche Med. Wochenschr.*, 1906, No. 51 (Supplement).

—— *Ibid.*, 1907, No. 2.

KROMAYER: *Biochimica e Therapia Sperimentale*, ii., No. 5.

—— *Berliner Klin. Wochenschr.*, 1910, No. 27, p. 1294.

—— "A Convenient, Painless Method of the Ehrlich-Hata Injection." *Ibid.*, No. 37, p. 1698.

—— "Ehrlich-Hata '606' in Ambulant Practice." *Ibid.*, 1910, No. 39, p. 1791.

—— "Theoretical and Practical Considerations of Ehrlich-Hata '606.'" *Ibid.*, 1910, No. 34, p. 1585.

LANDSBERGER: *Therapie der Gegenwart*, 1907, No. 3.

LANGE: "On the Acquirement of the Wassermann Reaction in Cases of Syphilis treated with Ehrlich's '606.'" *Berliner Klin. Wochenschr.*, 1910, No. 36, p. 1656.

LASSAR: *Ibid.*, 1907, No. 22.

LESSER, E.: "Textbook of Venereal Diseases." Tenth and Eleventh Editions. Published by Vogel.

—— "Treatment of Syphilis in the Light of the Results of Recent Research." Society for Internal Medicine, Meeting of June 10, 1907.

LOEB: "Experience with Ehrlich's Dioxydiamido-arsenobenzol ('606')." *Münchener Med. Wochenschr.*, 1910, No. 30, p. 1580.

MALINOWSKY: *Przeglad Chorob*, 1910, No. 8.

MAASS: *Berliner Klin. Wochenschr.*, 1907, No. 17.

MCDONAGH: *Lancet*, ii., No. 10, 1910.

MEIROWSKY: "The Effect of Ehrlich's Drug on the Syphilitic Process." *Med. Klin.*, 1910, No. 42, p. 1653.

MEIROWSKY AND HARTMANN: "Influencing the Symptoms of a Hereditarily Syphilitic Infant through the Serum of Patients who had previously been treated with Ehrlich's Arsenobenzol." *Med. Klin.*, 1910, No. 40, p. 1572.

MELTZER: *New York Med. Journ.*, lxxxii., No. 8.

METSCHNIKOFF AND ROUX: *Annal. de l'Institute Pasteur*, vol. xix., 1905.

MESNIL AND NICOLLE: *Ibid.*, 25, i., 1907.

MICHAELIS, L.: Demonstration before the Berlin Clinical Society on June 22, 1910. Reference in *Berliner Klin. Wochenschr.*, 1910, No. 28.

—— "A Hundred and Ten Cases of Syphilis treated according to Ehrlich-Hata." *Ibid.*, 1910, No. 37, p. 1695.

—— "The Subcutaneous Administration of the Ehrlich-Hata Syphilitic Preparation." *Ibid.*, 1910, No. 33, p. 1531.

MICHELI AND QUARELLI: *Corriere Sanitario*, 1910, No. 30.

MIEKLEY: "On the Effect of Atoxylate of Mercury on Human Syphilis." *Deutsche Med. Wochenschr.*, 1909, No. 41.

MILIAN: *Le procès médical*, 1910, No. 35.

MONDSCHEIN: *Wiener Med. Wochenschr.*, 1910, No. 36.

MOORE, NIERENSTEIN, AND TODEL: *Biochemical Journal*, 1907, ii., 324.

MOSES: *Berliner Klin. Wochenschr.*, 1907, No. 38.

MÜLLER: "On the Therapy of Primary Syphilitic Affection." *Med. Klin.*, 1910, No. 48, p. 1899.

MULZER, P.: "On the Appearance of Spirochætes in

Syphilitic and Other Infected Tissues." *Berliner Klin. Wochenscher.*, 1905, No. 36, pp. 1144-1149.

MULZER, P.: "Collective Reference on the finding of Spirochætes in Syphilis." *Arch. f. Derm.*, 1906, vol. lxxix., Nos. 2 and 3.

—— "On the Technique and Practical Value of the Wassermann Reaction." *Zeitschr. f. Immf.*, 1910, vol. v., Nos. 2 and 3.

—— AND MICHAELIS: "Hereditary Syphilis and the Wassermann Reaction." *Berliner Klin. Wochenschr.*, 1910, No. 30.

—— See CITRON.

—— See UHLENHUTH.

NEISSER, A.: "Experimental Syphilitic Research from its Present Position." Julius Springer, publisher, Berlin.

—— "On the Employment of Arsacetin (Ehrlich) in the Treatment of Syphilis." *Deutsche Med. Wochenschr.*, 1908, No. 35, p. 1500.

—— "On the New Ehrlich Drug." Open Letter to the Editor of the *Deutschen Med. Wochenschrift. Ibid.*, 1910, No. 26, p. 1212.

—— AND KUZNITZKI: "On the Significance of Ehrlich's Arsenobenzol for the Treatment of Syphilis." *Berliner Med. Wochenschr.*, 1910, No. 32, p. 1485.

NOCHT AND WERNER: *Deutsche Med. Wochenschr.*, 1910, No. 34.

NYSTRÖM: "Ehrlich-Hata Mixture." Björk and Börjesson, Stockholm, 1910.

OPPENHEIM: "On the Mercury-Fast Qualities of the Spirochætes of Syphilis, together with Remarks

on the Therapy with Ehrlich-Hata '606.'' *Wiener Klin. Wochenschr.*, 1910, No. 37, p. 1308.

PASINI : " On a Simple and Practical Method of Injecting the Ehrlich-Hata Preparation '606.'" *Münchener Med. Wochenschr.*, 1910, No. 47, p. 2461

—— *Corriere sanitario*, 1910, No. 30.

PICK : Imperial Medical Society, Vienna. Reference *Wiener Klin. Wochenschr.*, 1910, No. 26.

—— " Report on the Results up to the Present of the Treatment of Syphilis with the Ehrlich-Hata Preparation (120 Cases)." *Ibid.*, 1910, No. 33, p. 1193.

POLLAND AND KNAUR : " Report of Fifty Cases of Syphilis treated with Ehrlich-Hata '606.'" *Ibid.*, 1910, No. 43, p. 1521.

PRITCHARD, R.: "A Case presenting the Early Symptoms of General Paralysis with Recovery under Soamin." *Brit. Med. Journ.*, 1910, vol. i., p. 192.

RIEHL : " On the Treatment of Syphilis with Ehrlich's Remedy." *Wiener Klin. Wochenschr.*, 1910, No. 45, p. 1594.

ROSENTHAL : " On '606.'" *Berliner Klin. Wochenschr.*, 1910, No. 47, p. 2137.

RUELE : *Münchener Med. Wochenschr.*, 1909, No. 14.

RUMPEL : Reference *Med. Klin.*, 1910, No. 46, p. 1837.

SALMON, *Comptes Rendus Hebdom Soc. Biologie*, March 22, 1907.

—— *Ibid.*, April 19, 1907.

SALOMON : " Treatise on the Treatment of Syphilis with Ehrlich-Hata '606.'" *Med. Klin.*, 1910, No. 42, p. 1652.

SCHANZ: "The Ehrlich Preparation '606' in Diseases of the Eyes." *Münchener Med. Wochenschr.*, 1910, No. 45, p. 2344.

SCHAUDINN AND HOFFMANN, E.: "Current Report on the Presence of Spirochætes in Infected Syphilitic Tissue and in Papilloma." *Arbeiten aus dem Kaiserlichen Gesundheitsamte*, April 10, 1905, vol. xxii., No. 2, p. 527.

SCHAUDINN: "On the Spirochætic Result in the Juices of the Lymphatic Glands of Syphilitics." *Deutsche Med. Wochenschr.*, May 4, 1805, No. 18, pp. 711-714.

—— Demonstration before the Berlin Medical Society, May 17, 1905. *Berliner Klin. Wochenschr.*, 1905, No. 12, p. 694.

—— Conclusion of the Discussion at the Meeting of the Berlin Medical Society on May 24, 1905. *Ibid.*, 1905, No. 23, p. 733.

—— "On the *Spirochæta pallida* in Syphilis and the Difference of this Form compared to Other Kinds of this Genus." *Ibid.*, May 29, 1905, No. 22, p. 673.

—— "On the Knowledge of the *Spirochæta pallida*." *Deutsche Med. Wochenschr.*, October 19, 1905, No. 42, p. 1665, and No. 43, p. 1728.

—— "Reply to Attestation before us (Butschli's)." *Ibid.*, 1906, No. 2, p. 71.

—— Discussion Remarks, Fifteenth International Congress, Lisbon, April 19 to April 26, 1906. Reference *Derm. Zeitschr.*, vol. xiii., No. 8, p. 573.

SCHILD: *Berliner Klin. Wochenschr.*, 1902, No. 13.

—— *Derm. Zeitschr.*, 1903, x., No. 1.

SCHREIBER, E.: "On the Intravenous Injection of the Ehrlich Drug '606.'" *Münchener Med. Wochenschr*, 1910, No. 39, p. 2026.

—— AND HOPPE: "On the Treatment of Syphilis with the Newest Ehrlich-Hata Arsenic Preparation '606.'" *Ibid.*, 1910, No. 27, p. 1430.

SCHWABE: "On the Effect of Ehrlich's Arsenobenzol on Psoriasis and Lichen Ruber Planus." *Ibid.*, 1910, No. 36, p. 1877.

SCHWARTZ AND FLEMMING: "On the Behaviour of the Ehrlich-Hata Preparation, Arsenophenylglycin, of Iodide of Potassium, and of Sublimate, to the Wassermann Reaction." *Ibid.*, 1910, No. 37, p. 1933.

SELIGMANN AND CRONER: *Deutsche Med. Wochenschr.*, June 20, 1907.

SELLEI: "The Clinical Action of Ehrlich's Diamidoarsenobenzol ('606')." *Münchener Med. Wochenschr.*, 1910, No. 39, p. 2031.

SIESKIND: "Comprehensive Report of 375 Cases treated with the Ehrlich-Hata Preparation." *Ibid.*, 1910, No. 39, p. 2027.

SPATZ, A.: "Current Reports on Syphilitic Cases treated with the 'Therapia sterilisans magna' (Ehrlich-Hata Preparation)." *Wiener Med. Wochenschr.*, 1910, No. 17.

SPIETHOFF: *Münchener Med. Wochenschr.*, 1910, No. 35, p. 1822.

STRAUSS: "Early Treatment of the Primary Syphilitic Affection with Mercurial Applications and Cauterization." *Derm. Zentralbl.*, November, 1906.

TAEGE: "On the Successful Treatment of a Syphilitic Infant by treating its Nursing Mother with '606.'" *Münchener Med. Wochenschr.*, 1910, No. 33, p. 1725.

—— "Experiences and Observations with the Ehrlich-Hata Preparation '606' in the Treatment of Syphilis." *Ibid.*, 1910, No. 42, p. 2180.

THALMANN: "Syphilis and its Treatment in the Light of Recent Researches." April, 1906.

TOMASCZEWSKI: "Report given before the Charité Medical Society on June 2, 1910." *Berliner Klin. Wochenschr.*, 1910, No. 33, p. 1553.

TORDAY: "Report on the Ehrlich-Hata Treatment." *Wiener Klin. Wochenschr.*, 1910, No. 39, p. 1381.

TREUPEL: "Experiences and Considerations with the New Ehrlich-Hata Drug in Syphilitic and Meta-Syphilitic Diseases." *Deutsche Med. Wochenschr.*, 1910, No. 30, p. 1393.

—— "Further Experiences with Ehrlich-Hata Injections in Syphilitic and Meta-Syphilitic Diseases." *Ibid.*, No. 36, p. 1787.

TRUFFI: *Biochimica e Therapia Sperimentale*, ii., No. 5.

UHLENHUTH: Discourse at the Colonial Congress, 1910.

—— GROSS AND BICKEL: Researches as to the Effect of Atoxyl on Trypanosomes and Spirochætes." *Deutsche Med. Wochenschr.*, 1907, No. 4.

—— Discussion Remarks, Berlin Medical Society, February 13, 1907. *Berliner Klin. Wochenschr.*, 1907, No. 12, p. 349.

UHLENHUTH: Discussion remarks, Berlin Army Medical Society, March 21, 1907. Society's Minutes.

—— AND GROSS: "Researches as to the Effect of Atoxyl on Spirillosis of Fowls." *Arbeiten aus dem Kaiserlichen Gesundheitsamte*, vol. xxvii., No. 2, 1907.

—— Discussion Remarks, Berlin Medical Society, May 15, 1907. *Berliner Klin. Wochenschr.*, 1907, No. 22.

—— HOFFMANN AND ROSCHER: "Researches as to the Action of Atoxyl on Syphilis." *Deutsche Med. Wochenschr.*, 1907, No. 22.

—— Discussion Remarks, Society for Internal Medicine, June 24, 1907. *Ibid.*, 1907, No. 30.

—— HOFFMANN AND WEIDANZ: "On the Preventive Effect of Atoxyl on Syphilis induced Experimentally in Apes and Rabbits." *Ibid.*, 1907, No. 39.

—— AND WEIDANZ: "Researches as to the Preventive Action of Atoxyl in comparison to Mercury in Experimental Syphilis of Rabbits." *Ibid.*, 1908, No. 20.

—— AND MANTEUFEL: "Chemotherapeutical Experiments with Some of the New Atoxylic Preparations in Spirochætic Diseases, with Especial Reference to Experimental Syphilis." *Zeitschr. f. Immf.*, 1908, vol. i., No. 1.

—— "On the Effect of Atoxylate of Mercury in Spirochætic Diseases, especially in Experimental Syphilis." *Med. Klin.*, 1908, No. 43.

—— AND MULZER: Demonstration before the Berlin Medical Society on December 8, 1909. *Berliner Klin. Wochenschr.*, 1909, No. 51.

UHLENHUTH AND MULZER: Demonstration before the Berlin Medical Society on January 12, 1910. *Berliner Klin. Wochenschr.*, 1910, No. 4.

—— —— "The Experimental Bases of Chemotherapeutical Researches with the New Arsenic Preparations in Spirochæte Diseases, with Special Reference to the Treatment of Syphilis." *Deutsche Med. Wochenschr.*, 1910, No. 27.

——Discussion Remarks on Wechselmann's Discourse, Microscopic Society, May 20, 1910. Reference in *Zentralbl. f. Bakter.*, Supplement to Part I., vol. xlvii.

—— Discussion Remarks on the Treatment of Syphilis with the Ehrlich Preparation '606.' Natural Philosophers, Königsberg, September 21, 1910. *Deutsche Med. Wochenschr.*, 1910, No. 41.

—— Discussion Remarks on Roscher's Discourse to the Berlin Army Medical Society at the Meeting of November 21, 1910.

—— Inquiry into the Effect of Ehrlich's Arsenobenzol in Syphilis. *Berliner Med. Klin.*, 1910, Nos. 36, 37, 38, 39, 41, 43, 46.

VOLK: *Wiener Med. Wochenschr.*, 1910, No. 35.

WASSERMANN, A., AND BRUCK: "Is the Complement Formation on the Arise of Specific Deposit a Phenomenon which is dependent on the Precipitation, or the Effect of Amboceptors?" *Med. Klin.*, 1905, p. 1409.

—— *Münchener Med. Wochenschr.*, 1906, No. 49.

—— NEISSER, A., AND BRUCK, C.: "A Sero-Diagnostic Reaction in Syphilis." *Deutsche Med. Wochenschr.*, 1906, No. 19, p. 755.

WASSERMANN, A., AND SCHUCHT: "Further Report on the Proof of Specific Syphilitic Substance through the Anchoring of the Complement." *Zeitschr. f. Hygiene und Infektionskrankheiten*, 1906, p. 451.

—— AND PLAUT: "On Syphilitic Antibodies and Cerebrospinal Fluid in Paralysis." *Deutsche Med. Wochenschr.*, 1906, No. 44, p. 1768.

—— "On the Development and Present Position of the Sero-diagnosis in Syphilis." *Berliner Klin. Wochenschr.*, 1907, Nos. 50 and 51.

—— "The Sero-diagnosis of Syphilis and its Significance in Medical Practice." Congress for Internal Medicine, Vienna, 1908.

—— *Münchener Klin. Wochenschr.*, 1908, pp. 388 and 745.

—— M., AND MEIER, GG.: "On the Clinical Value of the Serum Reaction." *Deutsche Med. Wochenschr.*, 1907, No. 32.

WECHSELMANN: "On the Treatment of Syphilis with Dioxydiamidoarsenobenzol." *Berliner Klin. Wochenschr.*, 1910, No. 27, p. 1292.

—— Discourse given before the Berlin Medical Society at the Meeting of June 22, 1910.

—— *Derm. Zeitschr.*, 1910, xvii., No. 7.

—— *Deutsche Med. Wochenschr.*, 1910, No. 32, p. 1478.

—— "On Local and General Hyperæsthesia on the Employment of Dioxydiamidoarsenobenzol (Ehrlich '606')." *Berliner Klin. Wochenschr.*, 1910, No. 47, p. 2133.

—— AND LANGE: "On the Technique of Injection of Dioxydiamidoarsenobenzol." *Deutsche Med. Wochenschr.*, p. 1395, No. 30.

WECHSELMANN AND SEELIGSOHN : " On the Effect of Dioxydiamidoarsenobenzol on the Eye." *Deutsche Med. Wochenschr.*, 1910, No. 47, p. 2189.

WEINTRAUB : " Experience with the Ehrlich-Hata Syphilitic Remedy ' 606.' " *Med. Klin.*, 1910, No. 43, p. 1683.

WERNER, H. : " The Ehrlich-Hata Drug ' 606 ' in Malaria." *Deutsche Med. Wochenschr.*, No. 39, p. 1792.

WICHECKIEWICZ : *Przeglad Lekarski*, 1910, No. 39.

VON ZEISSL : *Wiener Med. Wochenschr.*, 1903, No. 17.

—— *Ibid.*, 1907, No. 24.

—— *Ibid.*, 1907, No. 33.

—— *Ibid.*, 1910, No. 32.

—— *Ibid.*, 1910, No. 34.

—— " Report on the Treatment of the First Hundred Cases with Ehrlich ' 606.' " *Ibid.*, 1910, No. 38, p. 2203.

ZERNIK : " Patent Charter for the Ehrlich-Hata Preparation ' 606.' " *Deutsche Med. Wochenschr.*, 1910, No. 37, p. 1716.

ZIELER : " Experience with Ehrlich-Hata ' 606.' " *Ibid.*, 1910, No. 44, p. 2040.

—— " Development and Results of the Modern Arsenic Therapy in Syphilis." *Münchener Med. Wochenschr.*, 1910, No. 47, p. 2461.

INDEX

Abdominal pain, 28
Abducens paralysis, 135, 186
Abortion after injection, 190
Absence of visual disturbances, 124
of patellar reflex, 179
Acceleration of pulse, 176, 188
Accommodation, paresis of, 123
Acetic acid, 58, 67, 86
glacial, 60
solution, 63
Acetyl combination, 29
Acid, acetic. See Acetic acid
carbonic, 64
para - amino - phenyl-arsenic, 12
solutions, 69, 81, 190, 192, 193
warning against injection of, 190
sulphanilic, 12
Acquired specific disease, 155
Action, indurating, 90
organotropic, 195
parasitotropic, 40
and secondary effects of "606," 50
toxic, 182
Acute nephritis, 191
syphilitic nephritis, 126
Adeps lanæ anhydricum, 68
Administration of atoxylate of mercury, 34
Adults, fatal cases in, 191
Advance in therapy of syphilis, 196
Advanced nervous disease, 202
paralysis, 131
vascular disease, 202
Affections, gangrenous, 83
indurated primary, 200
of nervous system, 194
primary, 2, 4, 5, 92-98, 144, 153, 154, 155, 156, 157, 159, 169
Affinity, neurotropic, 165
Air bubbles, 72
Albumin, 177, 179
Albuminuria, 35, 177
Alcohol, ethyl, 59
methyl, 54, 56, 57
Alkali, 62
Alkaline reaction, 59
solutions, 51, 53, 54, 67, 81, 155
Alt's method, 52, 53
Alypin, 85
Amaurosis, 124, 125
Amyloid, chronic, 126
Anæmia, 191, 192
Anæsthetic, 85
Anal papules, 90, 103, 159, 200
Anamnesis, 9
Angina, 99
specific, 90, 98, 153

Angina syphilitica, 22
Animal experiments, 4, 7, 34, 106
Animals, observations on, 48, 49, 68
Aniscoria, 186
Annular syphilides, 22
Antitoxines, 136
Anti-syphilitic action of atoxyl, 49
treatment, 8
Anus, 115, 157
Apes, syphilis of, 4, 20, 47
inoculation of, 48
Aphasia, auditory, 192
Apoplectic attacks, 193
Application, intramuscular, 81
subcutaneous, 81, 83
Arsacetin, 27-29, 40, 195
and blindness, 29
and deafness, 29
description of, 27
toxic action of, on optic nerve, 28
Arsenic, 138
Arsenic acid anilin, 12
action, cumulative, 203
deposit, 203
Arsenic-fast residue, 39
Arsenic intoxication, 192
neuritis, 189
preparations, 33, 37, 122, 199
residue, quinquevalent, 40
trivalent, 40
secretion of, 87
Arsenical preparations, injections of, 6
rheumatism, 178
Arsenicism, 189
Arsenobenzol, 48, 63, 105, 106, 108, 109, 110, 113, 116, 117, 118, 119, 120, 122, 123, 125, 126, 127,
Arsenobenzol—*continued*:
128, 129, 130, 131, 132, 133, 134, 135, 136, 144, 146, 149, 150, 156, 157, 158, 160, 161, 162, 164, 165, 168, 170, 171, 173, 174, 178, 184, 185, 187, 190, 195, 196, 199, 200, 201, 202, 203, 204
arresting effect of, 199
best effects of, 121, 122
effect on organism, 86-89
expectations of, 91
first report of, 89
neurotropic action of, 185
prophylactic power of, 48
therapeutic action of, 91, 92
toxic effect of, 195
value of, 197
when and how to use, 197
Arsenophenylglycin, 40-44, 46, 128, 203
chemical constitution of, 41
Arterio-sclerosis, 191, 192
Arteritis obliterans, 118
Assimilation, 86
Association of Internal Medicine, 30
Atonic ulcers, 160
Atoxyl, 6, 12-26, 37, 39, 40, 48, 49, 89, 112, 122, 125, 180, 195, 204
anti-syphilitic action of, 49
constitution of, 12, 13
effect of, 21-26
in human syphilis, 21
and mercury in syphilis, 30

Atoxyl, secondary effects of, 49, 125
spirillicide, action of, 49
in spirillosis of fowls, 18
and sublimate, continued application of, 29
toxic doses of, 23
toxicity of, 26
in trypanosome diseases, 30
Atoxylate of mercury, 29-37, 48, 89
administration of, 34
and rats, 31
secondary effects of, 34, 35
Atoxylic blindness, phases of, 25
resistance, 23
Atrophy of optic nerve, 28, 39, 124
optical, 186
of papilla of optic nerve, 25
of visual nerves, 24
Attacks, apoplectic, 193
epileptic, 42, 188
gastric, 130
of perspiration, 193
Attenuated solutions (intravenous injection), 56
Auditory aphasia, 192
nerves, 29, 195
organ, 187
Augmentation of diabetes, 190
Author and Citron, method of, 63, 64

Bandages, 86
Beads, glass, 53
Beard, papules in, 160
Behring's serum, 99
Benzine iodine, 72
Benzol nucleus, 15
Benzolsulphoneparamino-phenylarsenate of sodium, 37
Berkefeld's bougies, 14
Berlin Medical Society, 129, 133
Best effect of arsenobenzol, 121, 122
Bilateral specific iritis, 123
Bladder, paralysis of, 181, 182, 188
Blaschko, method of, 62, 63
Blindness, 24, 39
and arsacetin, 29
Blisters, pemphigous, 136, 138
Blood-corpuscles, 87
red, 177
Blood-pressure, diminished, 176
disturbances of, 133
increased, 176
Bone disease, 103
Bony processes, 116
Bruit, systolic, 176
Bubo, maxillary, 93
strumous, 97
Buccal mucous membrane, 156
Bulbar protuberance, 135
symptoms, 194
Bureau, Imperial Health, 16, 17, 29, 204
Buttocks, pain in, 81, 82

Cachexia, 194
Calcium carbonate, 64, 65
emulsion, 155
Calf of leg, 85
Calomel, 96, 111, 139
salve, 11
Cannula, Strauss, 79
Schreiber stopcock, 79
Carbonic acid, 64
Cardiac remedy, 133

Caries, 134
Cartilaginous primary forms, 93
Cases which failed to report themselves, 171
Catheter tap, Posner's, 78
Caustic soda, solution of, 50, 51, 52, 53, 54, 55, 67, 182
Cauterisation, 6
Central nervous organs, injury to, 24
system, diseases of, 132
Cerebral syphilis, 116, 117, 118, 127
headache of, 105
Cervical spinal cord, 195
Chancre, 6, 22, 47, 92, 96, 108
Chancres mixtes, 97
Charité Annales, 35
Charlottenberg United Chemical Works, 30
Chemical constitution of arsenophenylglycin, 41
Chemical Institute, Virchow Hospital, 88
Chemotherapeutical experiments, 33
Chemotherapy of spirilloses, 33
of syphilis, 12-204
Chorioiditis, 186
Choroid, exudative processes of, 124
Choryza, 134
Chronic amyloid, 126
intermittent treatment of syphilis, 7
Cicatrix, 47, 111
Circulatory apparatus, disturbance of, 133
Citron and Author, method of, 63, 64
Cleansing process, 93
Cocaine, 85
Colonial Congress, 29, 42
Colonies, 18
Combined application of atoxyl and sublimate, 29
Compressed mono-sodium, 51
di-sodium, 51
Compression, 195
Condition of visual nerves, 125
Condylomata, 99, 101, 136
Congenital iritis, 174
specific disease of cornea, 124
syphilis, 109, 133, 155
Conjunctivitis, 174
Constipation, 179, 184
Constitution of atoxyl, 12, 13
Constriction, 130
Contraction of vessels of retina, 25
of visual field, 186
Contra-indications, 201
Cord, cervical spinal, 195
spinal, 194
Cornea, disease of, 20
congenital specific disease of, 124
Corneal syphilis of rabbits, 31
Cortical softening, 194
Cranium, periostitic swelling of, 153
vault of, 116
Cubital vein, 52
Cumulative arsenic action, 203
Curative effect, momentary, 103
Cutaneous eruptions, 42
malignant syphilis, 116
Cutis, 170
desquamation of facial, 175
Cylinders, 177, 179
Cylinduria, 177
Cystitis, 194

Deafness and arsacetin, 29
labyrinth, 127
Death, 43
Deaths of syphilitic infants, 191
Decomposition, 182, 184
Degeneration, parenchymatosic, 193
Degenerative changes, 194
Deposit of arsenic, 203
Desquamation of facial cutis, 175
Destruction of spirochætes, 174
Detrusor paralysis, 180, 188, 189
Deutschen Medizinischen Wochenschrift, 18
Deviation of course of disease 169
Diabetes, augmentation of, 190
Diagnosis and Wassermann reaction, 9
serum, 7
Diarrhœa, 178
Dichlorate, 65
Dichlorhydrate, 69
Difficulty in hearing, 187
Diffusion, 176
Di-hydrochloride of diamidoarsenobenzol, 54
Diminished blood-pressure, 176
Dioxydiamidoarsenobenzol, 44-204
formula, 45
Diphtheritic surfaces, 99
Disappearance of primary symptoms, 93, 94, 95
of reflexes, 181, 182, 183, 185
spirochætes, 106, 107
Disease, advanced nervous, 202
of cornea, 20
Disease of intestinal tract, 176
kidney, 202
specific, 33, 163
vascular, 202
Diseased tissue, 3, 194
Diseases of central nervous system, 132
gummatous internal, 127
meta-syphilitic, 198
of mucous membrane, 99
optic nerve, 202
parasyphilitic, 132, 162, 198
of pharyngeal organs, 117
spirilla, 27
trypanosome, 15, 27, 39, 41
Disintegration of medullary sheath, 26
Di-sodium compound, 51
Distilled water, 54
Disturbances of blood-pressure, 133
of circulatory apparatus, 133
of heart's action, 176, 177
local, 81
optical, 38, 185
organic, 195
of speech, 192
of spinal cord, 180
vesical, 188
visual, 24, 25, 28
Dosage, 139-141
Dose of Hectine, 37
in intramuscular injection of fowls, 46
in intramuscular injection of apes, 47
in intravenous injection, 47
of apes, 47
of mercury, 5
Dosis efficiens tolerata, 41

Dosis maxima tolerata, 46
Dourine, 16, 29
Drastic mercurial treatment, 199
Drug exanthemata, 174
Dysarthria, 130
Dysphagia, 22
Dysphasia, 22
Dyspnœa, 190

Early stage of secondary syphilis, 98-110
treatment of syphilis, 5
Effect of arsenobenzol on primary, secondary, and tertiary syphilitic diseases, 89-139
arresting, 199
on heart's action, 69
preventative, 199
toxic, 203
Effects, secondary, 36, 37, 38, 43, 172-195
Efflorescences, specific, 108, 150
Ehrlich drug and pregnant women, 190
"Ehrlich-Hata," 6, 44, 46, 93, 102, 107, 108, 112, 118, 121, 122, 123, 129, 135, 138, 139, 141, 153, 155, 158
"606" 50
injection, 127
preparation, 45
therapy, innocuousness of, 173
treatment, 147
Ehrlich and intramuscular injection, 80
and intravenous injection, 80
Ehrlich's method, 55
Emaciation, 42, 43, 89
Embolic pneumonia, 190
Embolism, pulmonary, 190
Emulsion, 188
calcium carbonate, 155
Kromayer's, 65, 71
neutral, 72, 81, 82, 166, 190
Encapsulated foci, 166
Endotoxines, 135, 137, 174, 191
Epicrisis, 196-204
Epilepsy, 43, 132
Epileptic attacks, 42, 188
Episcleritis, 123
Errors with regard to application of mercury, 1
Eruption, 110
of roseola, 3
Eruptions, cutaneous, 42
maculo-papulous, 90
Erythema, 174, 175
Eschar, necrotic, 114
Ethyl alcohol, 59
Eusemin, 85
Examination, microscopic, 194
Exanthem, 153, 155, 156, 159, 175
exsudativum multiforme, 174
hæmorrhagic, 191
maculo-pustulous, 156
morbillous, 174
Exanthemata, 100, 101, 104, 105, 175, 200
drug, 174
hæmorrhagic, 102
papulous, 34, 134
Exciter of syphilis, 2
Expectations from arsenobenzol, 91
Experimental injection of rats, mice, rabbits, etc., 15
Experiments on animals, 4, 7, 34, 45-50, 106
chemotherapeutical, 33
preliminary, 189

Exudative processes of choroid, 124
of retina, 124
Eye trouble, 165
affections, hereditary syphilitic, 123
Eyes, 185

Facial papule, 159
nerves, 195
paralysis, 118, 131, 151
Fæces, 87
Failures, 158
Fall of hair, 169
Fatal cases, 191, 192, 193
in adults, 191
of pemphigus neonatorum, 191
Fever, 83, 173, 174, 175, 176, 191
First report of arsenobenzol, 89
Fistula, 156
Flatulence, 176
Florid specific symptoms, 147
syphilis, 44, 89, 168
Forms of application, 172
Fowler's solution, 14, 15
Fowls, spirillosis of, 17, 46, 48, 49, 106
Fresh syphilis, 198
Fuller's earth, 86
Fundus oculi, 25

Galloping syphilis, 35
Gangrenous affections, 83
Gastric attacks, 130
General infection, 3
reaction, 105
secondary effects, 172
treatment, when to begin it, 5
Genital papules, 159, 200
Giddiness, 28, 187
Glacial acetic acid, 60
Glands, lymphatic, 16
Glandular juices, 107
swellings, 94, 97, 200
Glass beads, 53
Gluteal muscles, 53, 83, 190
necrosis of, 192
region, 60, 65, 71, 72, 82
Gluteus, 190
Glycol, 54, 55
Göttingen Medical Society, 150
Granulation, 33, 84
Grey oil, 37
Gumma, 113, 118, 120
laryngeal, 117
of tonsil, 114, 117
Gummata, 37, 113, 114, 115, 116
infectiousness of, 10
of larynx, 113
multiple, 114
subcutaneous, 113
Gummatous infiltrations, 22
internal diseases, 127
processes, 35, 117
syphilis, 116
ulcer, 114
wounds, 113

Hæmorrhagic exanthem, 191
excrescences, 190
Hair, 87
fall of, 169
Hard palate, 115, 116
Hatà injection, 186
powder, 63
Headache, 22, 28, 102, 103, 130, 135, 185, 187
of cerebral syphilis, 105
Hearing, 185
difficulty in, 187
improvement in, 128
Heart troubles, 202,
Heart's activity, disturbance of, 176, 177
effect of, 69
Hectine, 37, 38

Hectine, dose of, 37
Hemianopsy, 188
Hemiplegia, 131
Hereditary syphilis, 133-139, 164, 198
failure of "606" in, 135
syphilitic eye affections, 123
Herxheimer reaction, 104, 105, 157
Hg, 93, 116, 121
salicylic injections, 66
Hoarseness, 99
Hollow needle, 52
Hot-air treatment, 6
water, 59
Human specific disease, 33
Hydrarg. atoxyl, 35
Hydrarg. sal, 111
Hydrargyrum oxycyanatum, 6
Hydrochloride salt, 50
Hyperæsthesia, 43
"Hyperideal '606,'" 57, 140
Hyperleucocytosis, 86
Hyperplasia, 99, 100
Hypersensibility, 203
Hypertrophic papules, 103

Icterus, 127, 190
Ictus immunisotoricus, 166
Idiocy, 43
Immunity, 11, 18
Imperial Health Bureau. See Bureau
Imperial University Polyclinique for Skin and Venereal Diseases, 204
Impetiginous syphilide, 156
Impetigo capitis, 22, 169
Improvement in hearing, 128
Incipient diabetes, 127
Increase in weight, 88
Increased blood-pressure, 176
Indurated primary affections, 200
Indurating action, 90
Induration, syphilitic, 32
Indurations, 92, 93, 94
Infantile syphilis, 134
Infected tissues of primary and secondary periods, 105
of experimental syphilis, 106
Infection, general, 3
local, 174
spread while disease is latent, 172
transmission of, 201
Infections, 6
Infectiousness of gummata, 10
Infiltrated foci, 166
Infiltrations, 34, 83, 84, 85, 113, 134, 157, 166
gummatous, 22
nettlerash-like, 175
Influence of syphilitic research upon mercurial therapy, 1-11
Influencing result of Wassermann reaction by arsenobenzol, 141-149
Inguinal gland, 157
Inhibition, involuntary, 184
voluntary, 184
Initial sores, 90
Injection, abortion after, 190
intragluteal, 134
intramuscular, 55, 58, 60, 69, 71-73, 82, 85, 87, 141, 163, 173, 203
intravenous, 57, 75-81, 87, 88, 121, 140, 154, 167, 173, 176, 178, 192
pain of, 36, 85
repetition of, 203, 204
seat of, 65, 85, 86
subcutaneous, 60, 69, 73-75, 88, 166, 174, 203

Injection, technique of, 71-81
Injections of arsenical preparations, 6
of mercurial preparations, 6
Hg salicylic, 66
Injury, 204
to central nervous organs, 24
of optic nerve, 125
Innocuousness of Ehrlich-Hata therapy, 173
Inoculation of apes, 48
Intercostal neuralgia, 130
Internal organs, 109
syphilis of, 126-128
Interruption of vestibular nerves, 187
Interscapular region, 69
Intestinal tract, disease of, 178
irritation of, 180
Intoxication, arsenical, 192
methylalcoholic, 182, 183
phenomena of, 28, 43, 193
of sleeping sickness, Togo form, 43
of sleeping sickness, East Africa form, 43
Intragluteal injection, 134
region, 189
Intramuscular application, 81, 82, 83
injection. See Injection
of fowls, dose in, 46
Intravenous application, 81, 82
injection. See Injection
attenuated solutions, 56
Schreiber and Hobbe's method, 58
Schreiber's method, 75-78
Intravenous injection of fowls, 47
incorporation, 68, 69
Inunction cure, 138
treatment, 159
Involuntary inhibition, 184
Iodide of potassium, 112
Iodine, 111, 120
benzine, 72
therapy, 119, 197
tincture of, 72
treatment, 115, 186
Iritis, 122, 123, 165
bilateral specific, 123
papulosa, 122
syphilitica, 23
Irritation of intestinal tract, 180
of sciatic nerve, 85
Iversen's method of intramuscular injection, 51
of intravenous injection, 51, 52

Jarisch Herxheimer reaction, 104, 105
Joints, pain in, 174
Juices, glandular, 107

Keratitis parenchymatosa, 122, 123
Kidney disease, 202
Kidneys, 37
effect of Ehrlich drug on, 177
Knees, pain in, 188
Königsberg Meeting of Natural Philosophers, 192
Kromayer's paraffin emulsion, 65-71
effect of, 70, 71

Labia, ulceration of, 90
Labyrinth deafness, 127

Late stage of secondary syphilis and tertiary syphilis, 110-119
Latent period, 201
specific disease, 157
stages, mercury in, 7
Laryngeal gumma, 117
Larynx, 115
tertiary syphilis of, 193
Lecithin, 86
Lecture to Magdeburg Medical Society, 89
Leg, calf of, 85
ulcer of, 120
Legs: increased paralysis of, 188; pain in, 188
Lesions, primary syphilitic, 4
Lesser clinique, 20, 34, 35, 134, 182
Lesser's handle, 72
Leucocytes, 87
Leucocytosis, 86
Leucoderma colli, 101
Levator palpebræ superioris, paralysis of, 185
Lightning pains, 129, 132
Lip, 155
papule of, 159
primary affection of, 93
Liquid paraffin, 66
Litmus-paper, 60
Liver, specific disease of, 127
tumour of, 60
Local disturbances, 81, 172
infection, 174
reaction, 105
secondary effects, 81
Locus minoris resistentiæ, 165
Loss of power, 193
Lüer syringe, 75
Lues cutanea maculosa, 134
præcox, 121
Lungs, 109
Lymphadenitis, 102, 107, 108, 109
Lymphatic glands, 16, 98, 156
Maculo-papulous eruptions, 90
exanthema, 22, 134, 156
Magdeburg Medical Society Lecture, 89
Magnesia usta, 133
Mal de caderas, 16
Malignant period, 198
syphilis, 23, 28, 35, 154, 158, 160, 163
and ulcerous tertiary forms respectively, 119-122
Manifest symptoms, 8, 171
syphilis, 196
mercury in, 7
Massage, 86
Maxillary bubo, 93
Medizinische Klinik, 135
inquiry of, 161
Medullary sheath, disintegration of, 26
Mental disease, 43
Mercurial paraffin emulsion, 65
plaster, 6
preparations, 33
injections of, 6
therapy, 104, 119, 197, 200
influence of syphilitic research upon, 1-11
treatment, 115, 147, 148, 169, 186
Mercurialised animals, milk from, 139
Mercury, 28, 30, 112, 119, 120, 145, 196, 198, 200
and atoxyl, 30
atoxylate of. See Atoxylate
results of, 34
direct remedy in latent stages, 6

Mercury, direct remedy in manifest syphilis, 7
in specific disease, 7
doses of, 5
errors with regard to application of, 1
general treatment, when to begin, 2
salicylic acid, 37
Meta-arsenic acid anilide, 12
Metamorphosis, regressive, 22
Meta- and para-syphilitic diseases, including tabes and paralysis, 128-133
Meta-syphilitic diseases, 198
Methæmoglobin formation, 88
Method, Alt's, 52, 53
Blaschko's, 62, 63
of A. Citron and the Author, 63, 64
Ehrlich's, 55
Iversen's, 51
of Michaelis, 58
of Schreiber and Hoppe, 56
of Spiethoff, 60, 61, 62
of Wechselmann, 54
and Lange, 59, 60
Methyl alcohol, 54, 56, 57, 182, 183, 184
alcoholic intoxication, 182, 183
Mice, experimental infection of, 15
relapsing fever of, 19, 45
Microscopic examination, 194
Milk from mercurialised animals, 139
Momentary curative effect, 103
Mono-dichlorhydrate, 81
-hydrochloride, 55
Mono-sodium compound, 51
Morbillous exanthem, 174
Morphia, 85
Mucous membrane, buccal, 156
diseases of, 99
plaques, 98, 99
Multiple gummata, 114
Münchener Medizinische Wochenschrift, 184
Muscles, bladder, weakness of, 130
gluteal. See Gluteal
of swallowing, weakness of, 130
Myocarditis, 192
Myxomatous tissue, 33

Nagana, 15
Narcotics, 86
Naso-labial folds, 156
Natural Philosophers, Königsberg Meeting of, 192
Nausea, 28, 176
Necessity for ophthalmological examination, 125
Necrosis, 42, 83, 84
of gluteal muscles, 192
Necrotic eschar, 114
Needle, hollow, 52
Negative phase, 148
reaction, 145, 146, 147, 151, 187
result, 141, 142, 143, 144, 167, 169
Nephritis, 28
acute, 191
sypnilitic, 126
Nerves, auditory, 29, 195
facial, 195
optic, 26, 123, 165, 204
diseases of, 202
phrenic, 194, 195
Nervous diseases, 140
symptoms, 180
system, 198

Nettlerash-like infiltrations, 175
Neuralgia, intercostal, 130
Neuralgic pains, 85
Neurasthenics, 85
Neuritis, arsenic intoxication, 189
optical, 123, 185, 186
specific, 165
Neuropathic affinity, 165
Neurotropic action of arsenobenzol, 185
Neutral emulsion, 58, 72, 81, 82, 166, 188
suspension, 59
Novocain, 85
Nucleus, benzol, 15
Nurse, wet, 137
Nursing mother and syphilitic infant, 136
Nutrient enema, 111
Nystagmus, 187

Observation period, 91, 168
extent of, 168
Observations on animals. See Animals
Oculi fundus, 25
Oculomotoric paresis, 185
Œdema, 194
Olive oil, 36
Opacity, vitreous, 186
Ophthalmological examination necessary, 125
Opisthotonus, 191
Opium, 86
Optic nerve. See Nerves
atrophy of. See Atrophy
toxic action of arsacetin on, 28
Optical atrophy, 186
disturbances. See Disturbances
neuritis. See Neuritis
Orchitis gummosa, 115
Organ, auditory, 187
Organic disturbances, 195
Organism, effect of arsenobenzol on, 86-89
Organotrophic, 40
action, 195
Organs, pharyngeal, 99
vital, 40
Os coccyx, pain in, 82
Ozæna syphilitica, 134

Pain, abdominal, 28
in buttocks, 81, 82
of injection, 36, 85
in joints, 174
in knees, 188
in legs, 188
lightning, 129, 132
neuralgic, 85
in os coccyx, 82
of pressure, 86
at seat of injection, 183, 184
shooting, 28
Palate, 115
hard, 115, 116
soft, 115
Pallidæ, 108
Palmar eminences, 157
Papilla of optic nerve, atrophy of, 25
Papules, 22, 90, 101, 107, 108, 115, 139, 155, 156, 157
anal. See Anal
in beard, 160
facial, 159
genital. See Genital
hypertropic, 103
of lip, 159
mucous, 159
of tonsil, 120
of vagina, 90
Papulous deposits, 161
exanthemata, 34
syphilide, 34, 134, 158, 159

Para-amino - phenyl - arsenic acid, 12
-arsanilic acid of sodium, 27
-arsonate Hg, 29
Paraffin emulsion, 190
Kromayer's, 65-71
mercurial, 65
liquid, 66
Paralysis, 17, 42, 128, 129, 132
abducens. See Abducens
advanced, 131
of bladder. See Bladder
detrusor. See Detrusor
of extensors, 189
facial. See Facial
flabby, 118
of legs, 188
of levator palpebræ superioris, 185
of peroneus, 189
progressive, 128, 132
of rectus internus, 185
respiratory, 195
spinal, 129, 130
Paralytic patients, 143
Paraplegia, 131
Parasites, 18, 40, 105
Parasitotropic, 40
action, 41
Parasyphilitic diseases. See Diseases
Parenchymatosic degeneration, 193
Paresis of accommodation, 123
oculo-motoric, 185
Paronychia, 101, 136
Parrot's pseudo-paralysis, 134
Patellar reflex, absence of, 179
Patients, paralytic, 143
specific, 143
tabetic, 143
Pemphigoidal syphilide, 133
Pemphigous blisters. See Blisters
Pemphigus neonatorum, 133, 134, 158
fatal cases of, 191
Penis, chancre on, 92
Period, early, 201
latent, 201
malignant, 198
primary, 198, 199, 200
secondary, 198, 199, 200
ulcerous tertiary, 198
Periostitic swelling of cranium, 153
Periostitis, 114, 116
Peroneus, paralysis of, 189
Perspiration, 87
Petri saucers, 66
Pharyngeal organs, 99
diseases of, 117
probes, 111
ulcer, 120
Pharyngo-laryngeal carcinoma, 192
Phases of atoxylic blindness, 25
Phenolphthaleïn, 58, 59, 60, 61
Phenomena of intoxication. See Intoxication
reactionary, 84, 174
retarded syphilitic, 114
tubero-serpiginous, 159
Phimoses, 95
Phrenic nerve. See Nerve
Physiological salt solution, 52, 57
Pigment, 34, 90
Plaques, 22, 107
mucous, 98, 99
Plaques muqueuses, 161
Plaut-Vincent's angina, 110
Pneumonia, embolic, 190
Positive reaction, 145, 146, 147, 148, 149, 151

Positive result, 8, 141, 142, 143, 144, 167, 169
Posner's catheter tap, 78
Post-mortem, 191, 193
Potency, 89
Power, loss of, 193
Pregnant women and Ehrlich drug, 190
Preliminary experiments, 33
Preparations, arsenic. See Arsenic
mercurial, 33
Preventative effect, 199
Primary affection. See Affections
disappearance of. See Disappearance
of lip, 93
reduction of, 93, 94, 95
inoculation of syphilis of rabbits, 5
period, 198, 199
and secondary periods, infected tissue in, 105
stage, 5
syphilis, 200
syphilitic lesions, 4
ulcer, 150
Processes, bony, 116
gummatous, 117
ulcerous, 113
Proctitis, 180
Progressive paralysis. See Paralysis
Proliferation tissue, 93
Prophylactic, best, 86
power of arsenobenzol, 48
Prophylaxis, 6, 11, 199
against relapses, 199
secondary diseases, 199
Prostitutes, 164
Prostration, 43
Protozoal diseases, atoxyl in, 16
Protuberance, bulbar, 135
Psoriasis palmaris, 101
palmarum, 22
plantaris, 101
Pulmonary embolism, 190
syphilis, 126
Pulp, spleen - liver - bone-marrow, 4
Pulse, acceleration of. See Acceleration
slowing of, 176
Puncture, seat of, 83
Pupils, reaction of, 186
retraction of, 186
Pure culture, 33
syphilis, 162

Quinquevalent arsenical residue, 40

Rabbits, corneal syphilis of, 31
experimental infection of, 15
syphilis of, 20, 33, 45, 46, 48
primary inoculation syphilis of, 5
Rats and atoxylate of mercury, 31
experimental infection of, 15
relapsing fever of, 19, 45
Reaction, alkaline, 59
general, 105
Jarisch-Herxheimer, 104
negative. See Negative
phenomena, 84
of pupils, 186
serum, 8
specific, 33
Wassermann, 5, 7, 8, 35, 44, 79, 124, 141, 143, 144, 145, 146, 147, 151, 157, 164, 169, 187

Reactionary phenomena, 174
Record syringe, 63, 75
Rectum, tenesmus of, 179, 180
syphilis of, 127
Rectus internus, paralysis of, 185
Red blood-corpuscles, 177
Reduction of primary symptoms. See Primary
Reflexes, disappearance of. See Disappearance
Region, gluteal. See Gluteal
interscapular, 69
intragluteal, 189
Regressive metamorphosis, 22
Relapse, 147, 203
prophylaxis against, 199
Relapses, 121, 149-172
Relapsing fever, 30, 31, 49
of mice and rats, 19, 45
spirilla of, 46
Repetition of injection. See Injection
Residue, arsenic-fast, 39
Resistance, atoxylic, 23
Respiratory paralysis, 195
Result, negative. See Negative
of Wassermann reaction, 9, 10
positive. See Positive
Results of atoxylate of mercury, 34
Retarded syphilitic phenomena, 114
Retching, 176
Retention of urine, 179, 181, 183, 184, 188
Retina, contraction of vessels of, 25
exudative processes of, 124
Retraction of pupils, 186
Rhagades, 134
Rheumatism, arsenical, 178
Rigor, 173
Roseola, 22, 92, 100, 104, 153, 157, 169
eruption of, 3
urticarial, 157, 158
urticata, 100
Rupiæ syphiliticæ, 101

Saddle-nose, 112
Salicylic acid mercury, 37
Saline solution, 61
Salt, hydrochloride, 50
Salts of sodium, 29
"Salvarsan," 50
Saucers, Petri, 66
Scarlatina, 175
Schreiber and Hoppe, method of, 56
Schreiber's method of intravenous injection, 75-78
stopcock cannula, 79
Sciatic nerve, 189
irritation of, 85
Sciatica, 85
Sclerosis, 94, 95, 96, 97
Sclerotic tissue, 32, 33
Scrotal tissue, 33
ulcers, 32
Scrotum, syphiloma of, 33
Seat of injection. See Injection
pain at, 183, 184
of puncture, 83
Secondary affections, 35
of atoxylate of mercury, 35
diseases, prophylaxis against, 199
effects. See Effects
of atoxyl, 49, 125
local, 81
period, early, 200

Secondary period of syphilis, 37, 198, 199
phenomena, 155
symptoms, 2
syphilis, 154, 160, 165, 200
early stage of, 98-110
Secretion of arsenic, 87
Septicæmia, 17
Septum, 111
Sero-diagnostic results, 143
reaction, 167
Serological examinations, 11
Serous fluid, 84
Serpigino-ulcerous syphilide, 115
Serum, 138
Behring's, 99
diagnosis, 7
reaction, 8
Shivering, 193
Shock, 194
Shooting pains, 28
Shoulder-blade, 60
Sickness, sleeping, 15, 16, 24, 42, 43
Side groupings, 45
"606," 44, 45, 46, 49, 50, 65, 66, 67, 78, 94, 95, 105, 107, 108, 113, 115, 116, 121, 122, 123, 124, 128, 129, 135, 137, 138, 139, 142, 146, 149, 153, 155, 160, 164, 165, 170, 171, 173, 181, 190, 193, 196, 198, 201
(*a*), 60
(*b*), 60
action and secondary effects of, 50
"hyperideal," 57
intramuscular injection, 55
solution of, 55
Skin, 87
Sleeping sickness. See Sickness
Slowing of pulse, 176
Soamin, 38
Sodii *p*-aminophenylarsonas, 38
Sodium, salts of, 29
Softening, cortical, 194
Solution, acetic acid, 61
Solutions, acid. See Acid
alkaline. See Alkaline
attenuated, 56
of caustic soda. See Caustic Soda
Fowler's, 14, 15
physiological salt, 57
saline, 61
of "606," 55
Sores, initial, 90
primary, 90
Specific angina. See Angina
disease. See Disease
acquired, 155
of liver, 127
mercury in, 7
efflorescences, 108, 150, 178
gravity, 178
meningitis, 117
neuritis, 165
patients, 143
reactions, 33
treatment, 2, 4, 171
and Wassermann reaction, 10
Speech, disturbances of, 192
Spiethoff's method. See Method
Spinæ iliacæ anteriores superiores, 72
Spinal cord, 194
disturbances of, 180
paralysis. See Paralysis
phenomena in tabes, 105
syphilis, 188

Spirilla, 47, 153
diseases, 27
of relapsing fever, 46
Spirillicide action of atoxyl 49
of "606," 109, 110
Spirilloses, chemotherapy of, 33
Spirillosis of fowls. See Fowls
atoxyl in, 18
dose of "606" in, 46
Spirit, 86
Spirochæta gallinarum, 17, 19
pallida, 3, 5, 33, 38, 104
Spirochætes, 6, 7, 17, 18, 19, 32, 33, 47, 48, 68, 105, 106, 122, 135, 136, 137, 147, 148, 156, 157, 159, 166, 167, 191
destruction of, 174
disappearance of, 106, 107
Spirochætic septicæmia of fowls, 31
Spirochætosis of fowls, 31
Spleen-liver-bone-marrow pulp, 4
Stage, primary, 5
Sterile water, 56, 57
Sterilisatio magna, 196
Sterilise, 41
Stomatitis, 35
Strauss cannula, 79
Strumous bubo, 97
Subcutaneous cellular tissue, 111
gummata, 113
injection. See Injection
method of, 73, 74, 84
Sulcus coronarius, 156
Sulphanilic acid, 12
Suppuration, 84
Surfaces, diphtheritic, 99
Surra, 15, 16
Suspension, neutral, 59
of solutions which are ready for use, 50
Suspicious symptoms, 170
Swellings, glandular, 200
Symptoms, bulbar, 194
manifest, 8
nervous, 180
secondary, 2, 4
Synechia, 123
Syphilides, 100, 101, 102, 140
annular, 22
gummatous, 116
papulous. See Papulous
pemphigoidal, 133
tuberculous, 22
tuberous, 114
Syphilidologists, 167
Syphilitic children, 145
disease, typical forms of, 4
diseases of the eyes, treatment with arseno-benzol, 122-126
induration, 32
infant and nursing-mother, 136
research, influence of upon mercurial therapy, 1-11
triumph of, 11
sequelæ, 131
tissues, 170
ulcers, 31
virus, 3, 4, 8, 165
Syphilis, 1, 19, 20
advance in therapy of, 196
of apes. See Apes
atoxyl in human, 21
and mercury in, 30
cerebral. See Cerebral
chronic intermittent treatment of, 7

Syphilis, congenital. See Congenital
cutaneous malignant, 116
early treatment of, 5
exciter of, 2
florid. See Florid
galloping, 35
gravis, 36
hereditary, 133-139, 198
human, 33
infantile, 134
of internal organs, 126-128
maligna, 36
malignant. See Malignant
manifest, 196
primary, 200
pulmonary, 126
of rabbits. See Rabbits
experimentally induced, 48
of rectum, 127
secondary. See Secondary
spinal, 188
tertiary, 28, 35, 37, 44, 109, 118, 154, 160
nasal, 113
testicular and cerebral, 115
therapy of, 34
ulcerosa præcox, 23
visceral, 127, 139
Syphiloma of scrotum, 33
Syringe, Lüer, 75
Record, 63
System, nervous, 198
vascular, 198
Systolic bruit, 176

Tabes, 128, 129, 132, 194
spinal phenomena in, 105
Tabetic patients, 143
Tabo-paralysis, 129
Tachycardia, 176
Technique of injection, 71-81
Temperature, high, 175
Tenesmus, 178, 183
of rectum, 179, 180
Tertiary and malignant forms, 106
nasal syphilis, 113
period, 198
syphilis. See Syphilis
of larynx, 193
ulcerous process, 153
ulcers, 22, 90, 115, 116, 118
Testicular and cerebral syphilis, 115
Therapeutic action of arsenobenzol, 91, 92
Therapia sterilisans magna, 41, 43
Therapy, iodine, 119, 197
mercurial. See Mercurial
of syphilis, 34
Thigh, ulceration of, 113
Thirst, 178
Thrombo-phlebitis, ulcerous, 118
Thrombus, 190
Thymol acetin, 156
Tincture of iodine, 72
Tissue, diseased, 3, 194
myxomatous, 33
proliferation, 93
sclerotic, 32, 33
subcutaneous cellular, 111
Tongue, 153
Tonsil, gumma of, 114, 117
Tonsils, 99
Toxic action, 182
doses of atoxyl, 23
effect, 203
of arsenobenzol, 195
Toxicity of atoxyl, 26
Toxines, 105

Transmission of infection, 201
Treatment, anti-syphilitic, 8
drastic mercurial, 199
general, when to begin, 5
hot air, 6
iodine, 115, 186
mercurial. See Mercurial
specific. See Specific
of syphilitic diseases of the eyes with arsenobenzol, 122-126
Tremor, 193
Triumphs of syphilitic research, 11
Trivalent arsenical residue, 40
Troubles, heart, 202
Trypanosome diseases. See Diseases
atoxyl and mercury in, 30
Trypanosomes, 16, 17
Tsetse fly, 16
Tubercle of lungs, 114, 115
Tuberculous syphilides, 22
Tubero - serpiginous phenomena, 159
Tuberous syphilides, 114
Tumour of liver, 160
Typical forms of syphilitic disease, 4

Ulcer, pharyngeal, 120
of leg, 120
Ulcera dura, 94
Ulceration of thigh, 113
Ulcerations, 22, 117, 158
on labia, 90
Ulcerous, tertiary period, 196
thrombo-phlebitis, 118, 119
Ulcers, 33, 37, 111, 112, 113, 156
atonic, 160
Ulcers, scrotal, 31
syphilitic, 31
tertiary. See Tertiary
Ulcum durum conjunctivæ, 123
Ulcus molle, 97
United Chemical Works, Charlottenberg, 30
Urine, 87, 88
diminution of, 177, 178
retention of. See Retention
Urobilinuria, 87
Urticaria, 175
Urticarial roseola, 157, 158
Uvula, 112, 113

Value of arsenobenzol, 197, 198
of mercury, 2
Vascular system, 198
Vaseline oil, 68
Vault of cranium, 116
Vein, cubital, 52
Vertigo, 176, 185, 187
Vesical disturbances, 188
Vesicles, 42
Vestibular nerves, interruption of, 187
Virchow Hospital, Chemical Institute of, 88
Virus, 4
syphilitic. See Syphilitic
Visceral syphilis, 127, 139
Visual disturbances, 25, 28
absence of, 124
field, contraction of, 186
nerves, atrophy of, 24
condition of, 125
Vital organs, 40
Vitreous opacity, 186
Voluntary inhibition, 184
Vomer, 111
Vomiting, 28, 176
Vulva, 115

Warning against injection of acid solutions, 190
Wassermann reaction. See Reaction
and diagnosis, 9
negative result of, 9, 10, 141, 142
positive result of, 5, 141, 142, 143, 157
and specific treatment, 10
Water, distilled, 54
Water, hot, 54
sterile, 56, 57
Weakness of muscles of swallowing, 130
of bladder, 130
Wechselmann's method, 54
and Lange, method of, 59, 60
Weight, increase in, 88
Wet nurse, syphilitic, 137
When and how to use arsenobenzol, 197
Wounds, gummatous, 113

AUTHORITIES REFERRED TO

Alt, 43, 45, 50, 52, 53, 68, 69, 85, 87, 89, 90, 91, 92, 127, 129, 130, 140, 143, 176, 183, 190
Arndt, 204
Aschaffenburg, 116
Assmy, 78, 80
Auscherlick, 124, 145

Balzer, 21, 37
Bardachzi, 87
Bayet, 83, 119, 178
Behring, 99, 131, 188, 190
Bergarth, 36
Bering, 144, 154, 159, 162, 177, 178
Bertheim, 12, 13, 45, 46
Bettmann, 162, 178
Bickel, 17, 18
Birch-Hirschfeld, 26
Blaschko, 36, 62, 74, 104. 168
Blumenfeld, 97, 99, 103
Blumenthal, 11, 15
Boas, 11
Boethke, 36
Bohač, 151, 179, 180, 181, 183, 188
Bonhöffer, 188
Borcher, 29
Brandenburg, 101
Brändle, 87, 100, 103, 120, 145, 152
Breinl, 15
Bressler, 112
Broden, 16
Browning, 27
Bruck, 11
Bruhns, 101, 103, 108, 145, 164
Buschke, 104, 165, 185, 189

Chrzelitzer, 94, 100, 104, 117, 163, 189
Citron, 70, 149
Clingestein, 87, 100, 103, 120, 145, 152
Cohn, 165
Colle, 11

Darier, 21, 23
Dennecke, 96, 100, 153
Dobrowicz, 137
Dörr, 93, 100, 102, 120, 131, 182
Dreuw, 83, 164
Duhot, 90, 127, 131, 137, 153, 190

Ehler, 193, 196, 198, 199
Ehrlich, 12, 13, 16, 23, 27, 29, 33, 34, 39, 40, 41, 43, 44, 45, 46, 49, 50, 55, 69, 80, 81, 91, 92, 104, 108, 114, 116, 117, 126, 128, 129, 137, 139, 140, 141, 146, 147, 148, 149, 151, 159, 166, 167, 168, 170, 177, 180-183, 184, 193
Eitner, 155, 161, 184

Fabry, 36
Fauser, 181
Fehr, 123
Feldmann, 29
Finger, 10, 11, 21, 175, 177, 182, 185, 186, 187, 190, 195
Fischer, W., 88, 121, 152, 159, 165, 185, 189, 199
Fränkel, 67, 94, 99, 101, 102, 120, 127, 134, 143, 159, 174, 192
Friedländer, 117, 131, 155
Fürbringer, 72
Fürth, 108

Gennerich, 95, 100, 118, 121, 127, 142, 146, 154, 163, 176
Gerber, 109
Géronne, 94, 95, 98, 101, 102, 115, 127, 131, 144, 150, 153, 159, 165, 173, 176, 177, 178
Gesser, 116
Glaubermann, 19
Glück, 97, 99, 106, 113, 122, 131, 144, 152, 159, 175, 190
Grassmann, 202
Gross, Emil von, 18, 183
Grósz, 123
Grouven, 67, 94, 99, 101, 102, 108, 119, 120, 127, 132, 134, 139, 143, 155, 159, 162, 174, 192

Halberstädter, 96, 103, 104, 145, 163
Hallopeau, 21, 38
Hammer, 29
Hartung, 159
Hata, 33, 45, 46, 47, 49, 68, 106, 185, 186
Hauck, 21, 170, 181
Hecker, 108
Heinrich, 29
Hermann, 145
Herxheimer, 69, 94, 104, 109, 114, 120, 143, 154, 161, 175, 188, 191
Heuber, 88
Heymann, 28
Hoffmann, 4, 5, 6, 10, 20, 21, 102, 103, 104, 107, 119, 134, 151, 159, 176, 190, 192, 199
Holländer, 5
Hoppe, 50, 55, 56, 68, 86, 88, 142, 150, 190, 191
Hübener, 17, 29
Hüggenberg, 94, 98, 101, 102, 115, 150, 173, 178

Igersheimer, 124
Isaac, 98, 101, 115, 145
Iversen, 51, 69, 93, 94, 100, 107, 113, 140, 142, 148, 159, 173, 176, 178, 191

Jadassohn, 95, 161
Jakoby, 15
Jenssen, 28
Johnston, 39
Joseph, 155
Juliusberg, 93, 101, 119, 162
Junkermann, 67, 69, 72, 134

Kalb, 134, 138
Kaur, 188
Klausner, 87
Klemperer, 28
Knaur, 165
Koch, Robert, 16
Kopke, 16
Köster, 26
Kowalewski, 165
Kraus, 21
Kreibich, 21, 182
Kromayer, 65, 70, 73, 84, 100, 103, 113, 144, 152, 163, 176
Kusnitzki, 151

Lambkin, 36, 39
Landsteiner, 10, 11
Lange, 59, 74, 87, 141
Lassar, 21
Ledermann, 101, 104, 114, 119, 131, 153, 163, 176
Lesser, E., 2, 21, 35, 36
Lesser, F., 126
Lilley, 130
Linser, 144, 154, 161, 181
Lipschütz, 101, 102, 103, 104, 147, 159, 177
Loeb, 67, 88, 145, 151, 190

McDonagh, 142, 162
Manteufel, 30
Marchoux, 17
Marenesco, 138
Meirowsky, 70, 115, 121, 127, 138
Mesnil, 16
Metschnikoff, 11
Michaelis, L., 11, 58, 59, 60, 69, 73, 74, 84, 95, 100, 112, 126, 131, 133, 143, 145, 162, 182
Miekley, 34, 35, 93, 94, 98, 99, 100, 101, 118, 119, 145, 155
Moore, 30
Moses, 21
Mouneyrat, 37
Mulzer, 33

Nagelschmidt, 21
Neisser, A., 4, 7, 10, 11, 20, 27, 28, 38, 47, 68, 86, 93, 103, 104, 105, 132, 144, 148, 150, 151, 172, 173, 174, 176, 182, 199
Nicolle, 16
Nierenstein, 30

Oppenheim, 108
Orth, 192

Paderstein, 28
Passini, 67
Pflughöft, 29
Pick, 96, 120, 134, 142, 145, 177, 189
Pinkus, 94, 98, 159, 162, 178, 190
Plaut, 138
Pollack, 188
Polland, 165
Pritchard, 39
Profata, 11

Rapiport, 21
Raven, von, 43, 203
Raubitschek, 137
Ricord, 11
Rille, 96, 100, 154, 162, 174, 176, 181, 188, 190
Rodheim, 16
Roscher, 19, 21
Rouvière, 21
Roux, 11
Ruele, 29
Rumpel, 110

Saalfeld, E., 67, 101, 104, 163, 174
Sabotka, 151, 179, 180, 181, 183, 188
Salimpeni, 17
Salmon, 21, 27, 131, 140
Schanz, 24, 123
Schaudinn, 17
Scherber, 21
Scherschmidt, 42
Schindler, 96
Schlesinger, 133, 145, 174, 176, 177, 188
Scholtz, 106, 126, 138, 145, 159, 163
Schreiber, 50, 55, 56, 68, 75, 78, 79, 80, 89, 93, 101, 106, 132, 140, 142, 150, 154, 163, 173, 175, 176, 190, 191

Schulz, 96, 97, 162, 178
Seeligsohn, 123
Sellei, 106, 182
Sieskind, 69, 74, 83, 84, 97, 100, 102, 103, 105, 106, 121, 122, 189
Solomon, 94
Sowade, 25, 27, 28
Spatz, 82, 94, 100, 101, 175, 178
Spiethoff, 60, 61, 68, 73, 95, 98, 100, 102, 106, 113, 134, 143, 159, 174, 176, 161, 181
Stern, 96, 144, 155, 158, 159

Taege, 135, 136, 137, 160
Thalmann, 5
Thomas, W., 15, 16
Tomasczewski, 11, 47, 106
Torday, 130, 140, 145
Treupel, 87, 123, 131, 159, 162
Truffi, 104, 139

Uhlenhuth, 4, 11, 14, 16, 17, 18, 19, 20, 21, 24, 27, 29, 30, 32, 33, 34, 42, 45, 48 49, 106, 196, 204
Ulrich, 42

Volk, 101, 102, 103, 104, 147, 159, 177

Wassermann, 145, 146, 147
Weber, 117, 127, 142, 154
Wechselmann, 54, 59, 69, 73, 74, 85, 88, 91, 92, 93, 100, 101, 110, 111, 112, 115, 123, 124, 125, 127, 130, 133, 135, 141, 148, 149, 150, 152, 158, 162, 165, 166, 168, 171, 174 176, 188, 189, 190, 191
Weidanz, 20, 21
Weintraub, 78, 140, 199
Welander, 95, 101, 164
Woithe, 17, 29
Wolff, 152
Wolters, 104, 116, 127

Zeissl, von, 21, 93, 97, 116, 123, 131, 133, 139, 142, 164, 176
Zieler, 37, 119

REBMAN LIMITED, 129, SHAFTESBURY AVENUE, LONDON, W.C.

RC 201
M912
Mulzer
Therapy of Syphilis
Annex